Medical Library

JUL 11 1946

THE JOURNAL OF CLINICAL ENDOCRINOLOGY

VOLUME 6 NUMBER 6

JUNE, 1946

THERAPY WITH AQUEOUS SUSPENSIONS OF TESTOSTERONE 415
E. L. Sevringhaus and Stella Sikkema

DIETHYLSTILBESTROL IN AQUEOUS SUSPENSION 420
S. C. Freed

TESTOSTERONE PELLET IMPLANTATION 423
Joseph Eidelsberg

A CASE OF PRIMARY AMENORRHEA 426
Grete Stohr

THE XENOPUS TEST IN TUMOUR OF THE TESTIS 434
D. R. Meiring and H. Zwarenstein

BOOK REVIEW 441

ABSTRACTS OF CURRENT ENDOCRINE LITERATURE 442

PROGRAM OF THE TWENTY-EIGHTH ANNUAL MEETING 451

Issued monthly for The Association for the Study of Internal Secretions by Charles C Thomas, Publisher. Annual subscription, $6.50; single copies, $1.00

Why No Odor?

Unlike ordinary thyroid, Proloid is chemically separated from unwanted animal substances. Its lack of odor is the simplest demonstration of this difference between Proloid and ordinary desiccated thyroid. Proloid is a highly purified thyroid performing the function of thyroid medication in a more predictable manner.

Why a Metabolic Test? The usual (chemical) method of assaying thyroid does not always assure a product of constant metabolic potency.[1,2] Therefore, a biological assay is used to standardize the metabolic activity of Proloid. The U.S.P. method is also used.

Dosage: Proloid is used wherever thyroid is indicated, in the same dosages as U.S.P. In ¼, scored 1 and scored 5 grain tablets.

[1] Harrington, C. R.: "The Thyroid Gland," Oxford, 1933, p. 141.
[2] Meyer, A. E., and Wertz, A.: Endocrinology 24: 806, 1939.

PROLOID the improved thyroid

The Waltine Company NEW YORK 22

The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 6 JUNE, 1946 NUMBER 6
Copyright 1946 by the Association for the Study of Internal Secretions

THERAPY WITH AQUEOUS SUSPENSIONS OF TESTOSTERONE

E. L. SEVRINGHAUS, M.D.[1] AND STELLA SIKKEMA, M.D.

From the Department of Medicine, University of Wisconsin, Madison

TREATMENT of hypogonadism in males has been carried out with testosterone propionate and with methyl testosterone. The pure steroid, testosterone, has been used also in pellet form by implantation. Recently aqueous suspensions of estrogenic steroids have been employed in treating women in the climacteric. A trial of a similar suspension of pure testosterone was undertaken. The preparation used contained 20 mg. testosterone in 1 cc., and was furnished in sealed glass ampoules.[2] Prior to removal into the syringe for intramuscular injection the content of the ampoule was agitated vigorously by hand to assure a uniform suspension. No pain was experienced by the patients, and no local reactions were observed. Patients learned with ease to make their own injections. The results are illustrated herein by reports of a series of five men who were treated for hypogonadism due either to a delayed development or to the climacteric.

Case 1, D.F., Wis. Gen. Hosp. *No. 126402*, aged 18, was referred because of delayed adolescent development which had led to his rejection by the Selective Service Board. He had been unstable in school and unable to hold employment. He showed no development of facial, axillary or pubic hair, and the genitalia were preadolescent in size and type. His actions were spoken of as juvenile or feminine. Height was 162 cm., weight, 51 kg., blood pressure, 96/70 mm. Hg. Physical examination otherwise was within normal limits. Basal metabolic rate was plus 24 per cent; serum cholesterol, 188 mg. per

Received for Publication, April 2, 1946.

[1] Present address: Hoffman, LaRoche, Inc., Nutley, N.J.

[2] Grateful acknowledgment for a supply of testosterone suspension is made to Mr. P. E. Sprague of the Glidden Co., and Dr. C. Neilsen of the Abbott Laboratories.

100 cc. X-rays showed the femoral epiphyses ununited; bone age was estimated at $14\frac{3}{4}$ years. The sella turcica was slightly small. No gonadotrophic hormone could be found in two, twelve hour, night urine specimens.

The patient was treated with anterior pituitary growth promoting extract[3] hypodermically in doses of 1 cc. daily for four months without showing a definite increment of growth. When re-examined one year later his height was 165 cm.; weight, 54 kg., and there was no other important change in either history or physical examination. He was treated next with equine gonadotrophic hormone,[4] receiving 70 doses of ten units in each dose on alternate days, without obvious result. Subsequently he was treated with anterior pituitary gonadotrophic hormone,[5] receiving 25 Hisaw-Fevold units daily for 100 doses. No obvious benefit occurred.

Following this the therapy was changed to an aqueous suspension of testosterone,[6] in doses of 20 mg. twice weekly for nine weeks. He developed a more mature attitude and a more definite interest toward girls. He secured and held steady employment, and on reexamination three months after stopping therapy, the penis had enlarged somewhat, the prostate was firm and palpable, a slow growth of hair had shown itself on his face and pubic areas, and he reported an increased frequency of erections. Throughout the entire period of treatment there had been a very gradual deepening of the register of the voice which had become typically adult at the last examination.

Case 2, H.T., Wis. Gen. Hosp. *No. 117736*, was referred at the age of 53 because of fatigue which interfered seriously with his work as a veterinary. He had epigastric discomfort, bloating, and felt the need for eating between meals because of his fatigue and weakness. He complained also of dyspnea, paresthesias, a marked reduction in libido, and of premature ejaculations. Glycosuria had been found but was demonstrated to be an emotional hyperglycemia and glycosuria, with normal sugar tolerance test. Test of renal capacity for excreting potassium and retaining sodium definitely eliminated adrenal insufficiency. Physical examination was remarkable only in showing a soft left testicle with scarred left epidydimus. Blood pressure was 106/74 mm. Hg.; weight, 75 kg.

He was treated with testosterone propionate in oil, 25 mg. intramuscularly, at intervals of three times weekly, decreasing gradually to once weekly, with very distinct benefit. A change was made to the use of testosterone ointment, 25 mg. being introduced by inunction once weekly. The results were not satisfactory. Therapy was changed to methyl testosterone, 10 mg. orally daily, and did not feel satisfied with the results. He returned to the use of testosterone propionate 25 mg. every three days and was well satisfied for many months. Subsequently therapy was changed to aqueous suspension of testosterone, 20 mg. being injected intramuscularly once weekly. After a year on this routine he reported that he felt entirely comfortable so long as he took his medication. Intervals longer than one week were definitely associated with return of his previous symptoms. Blood pressure was 120/70 mm. Hg., and his weight had gone up during the program on aqueous testosterone from 75 kg. to 83 kg. while he continued with his usual veterinary work.

Case 3, L.W.F., Wis. Gen. Hosp. *No. 223662*, was referred at the age of 46 because of weakness, vertigo, decreased libido, marked morbid melancholy with frequent weeping

---

[3] *Phykentrone*, (Squibb).
[4] *Gonadogen*, (Upjohn).
[5] *Gonatrope*, (Straub).
[6] (Abbott).

for about four years, irritability, and hot flashes. He had a tendency to worry that he was becoming insane, and complained of subjective inadequacy to continue with his employment. Past medical history included a thoracotomy for empyema with good results. Physical examination showed weight, 66 kg.; blood pressure, 104/76 mm. Hg.; and he had a low grade chronic prostatitis.

Assay of 12 hour, night, urine specimens for gonadotrophic hormone showed no definite increase compared with normal levels, *i.e.*, he did not present the hormonal change characteristic of the climacteric.

He was treated with prostatic massage and chemotherapy and was given aqueous suspension of testosterone, 20 mg. daily for five doses, and then the same dose twice weekly. Marked subjective improvement occurred although the relief from the prostatitis was only gradual. By his own criteria he found that injections were necessary at intervals of not more than four days. When the interval became five days or longer there was a return of all the previous symptoms. Blood pressure was 116/88 mm. Hg. Weight rose, without attempt at dietary change, to 73 kg., and he was able to return to steady employment. Therapy was changed to the use of methyl testosterone, 10 mg. daily orally, and subjective benefits were maintained.

Case 4, E.K., Wis. Gen. Hosp. *No. 242671*, was seen at the age of 51, complaining of fatigue, weakness, hot flashes, sweating, dyspnea on exertion, nervousness, paresthesias, headaches, and a sense of epigastric fulness and constipation. With a height of 187 cm., his weight of 96 kg. represented a moderate obesity of long standing. Physical examination showed slight sclerosis of retinal vessels, a soft systolic murmur at the apex, a blood pressure of 108/76 mm. Hg., and no other significant abnormal findings. The patient complained of distinct decrease of libido within the past year. Laboratory findings were within normal limits. He was treated with aqueous suspension of testosterone, 20 mg. twice weekly for two weeks and thereafter once weekly. No dietary limitations were attempted. He gained 6 kg. and at the end of two months reported he was markedly improved so far as all his complaints were concerned. He was provided with sufficient material to continue treatment at 10 day intervals for three months.

He did not return until seven months later by which time he had discontinued therapy and his previous symptoms had returned. Because of his complaint of dyspnea on exertion attention was directed chiefly to his heart by the physician who examined him. Electrocardiogram at this time (not previously taken) was reported as indicative of advanced myocardial degeneration probably on a coronary sclerotic basis, with auricular and nodal premature contractions. He had no physical signs of congestive failure. We did not learn of his return to the hospital. He was not given further testosterone but was advised to reduce weight and to use aminophyllin 200 mg. four times daily.

Case 5, H. K., Wis. Gen. Hosp. *No. 129438*, was seen at the age of 63 complaining of fatigue, polyphagia, polydypsia, polyuria, nocturia, loss of 6.5 kg. in one month, drowsiness, somnolence and occasional cramps in the calves. There had been mild vertigo for a year, slight dyspnea and cardiac consciousness after exercise. Physical examination was not remarkable except as follows: blood pressure was 140/70 mm. Hg.; liver was distinctly enlarged with the border at about the level of the umbilicus; the spleen was enlarged to about five cm. below the costal border and slightly tender. The skin was dry. With glycosuria and the blood sugar of 350 mg. per cent, a diagnosis of diabetes mellitus was obvious. Treatment was carried out with a weighed diet, supplemented with protamine insulin. Distinct clinical improvement followed.

During subsequent months he developed insomnia and had a rather poor endurance

for muscular exercise to which he had been accustomed. He noticed paresthesias in the legs, hot flashes, choking sensations, occasional palpitation, a morbid tendency to feel discouraged and to lack enthusiasm for his usual occupations or for friendly contacts. Libido had disappeared. Physical examination showed regression of the hepatomegaly and splenomegaly toward normal limits. Rectal examination showed slight hemorrhoidal dilatation and the prostate was tender but not enlarged.

Eight months after beginning therapy for diabetes and at the time when the diabetes was under strictly good control therapy with methyl testosterone, 10 mg. daily orally was started. An increase to twice daily caused occasional erections, some improvement in muscular endurance but no improvement in mental symptoms. An increase to 30 mg. daily caused further distinct improvement without libido, however. After four months therapy was changed to aqueous testosterone, 20 mg. daily intramuscularly. He found prompt and lasting benefit from this therapy, deciding at first on an interval of from five to seven days between injections. He was more comfortable than on oral methyl testosterone. Libido was not significantly increased, erections were not bothersome, and he was essentially free from symptoms. This therapy was continued for 12 months with the interval usually four days between injections. On longer intervals the previous symptoms began to return after the fifth day. With such therapy this blood pressure varied from a maximum of 160/86 mm. Hg. to minimum of 145/90 mm. Hg., and was 150/90 mm. Hg. when he was two weeks without therapy. No essential change occurred in the management of the diabetes under hormone therapy.

DISCUSSION

Case 1 shows typical refractory testes which respond poorly to gonadotrophic therapy, and in this situation substitution with testosterone offers the only prospect at present of clinical benefit, granting that there is no probability of establishing fertility. It is known that testosterone propionate or methyl testosterone will induce a growth of the penis and the accessory organs, as well as the development of the secondary sex characteristics. The same goal can be achieved by use of aqueous suspension of testosterone crystals. The dose and the interval between injections must be determined by observation of the rate of progress in any case, as with other preparations.

Cases 2 to 5 are clinically typical of the climacteric syndrome in males. Comparisons of aqueous testosterone with the other methods of treatment are possible in *Cases 2 and 5*. The benefits are equally good with either the aqueous suspension or the oil solution of the propionate. The time interval from one injection until the subjective need for another was about the same with either preparation, viz.: one week in *Case 2* and from four to five days in *Case 5*. It has been possible to provide relief from the mental and autonomic symptoms without advancing the dose to a level which causes frequent erections or distinct increase in libido. These results have followed use of larger doses in other patients we have treated with testosterone propionate.

In *Case 3* the lack of gonadotrophic hormone increase in the two, night,

urine samples examined raises a question of the truly climacteric nature of the syndrome. Although we agree with the experience reported by Heller and Myers (1) that gonadotrophic hormone excretion is regularly increased in the climacteric, we can suggest merely that this patient had the symptoms and responses characteristic of the male climacteric. The occurrence of a chronic prostatitis in the climacteric is frequent enough so that we consider it a sequel to reduced testicular stimulation of the prostate rather than a cause of the symptoms.

In *Case 4* we regret the inability to continue the observations, but hope that after a trial of vasodilator therapy it may be possible to undertake a second course of testosterone to decide whether the response is again as good as before. It is well known that testosterone has provided subjective relief for men with anginoid pains. The effects have been thought due to coronary dilatation and improved myocardial status.

SUMMARY

An aqueous suspension of testosterone crystals injected intramuscularly in doses of 20 mg. provides a satisfactory replacement therapy in male hypogonadism. The apparent period of effective supply of testosterone from each injection is from four to seven days.

REFERENCE

1. Heller, C. G. and G. B. Myers. The male climacteric: its physiology, symptomatology, diagnosis and treatment. *J. Clin. Investigation. 21:* 622 (1942).

DIETHYLSTILBESTROL IN AQUEOUS SUSPENSION

S. C. FREED, M.D.

From Department of Medicine, Mt. Zion Hospital, San Francisco, California

A LARGE proportion of the preparations of sex hormones, both male and female, which are intended to be administered parenterally are dissolved in vegetable oil. While therapy with these preparations is both practical and satisfactory, there is a disadvantage to their administration in the fact that due to the oil vehicle there is a significant incidence of allergic or irritating action at the site of injection. These local reactions are not infrequent, and depend upon the type of vegetable oil used as a vehicle. The oils customarily used are derived from sesame, peanut or corn, and the incidence of reactions due to some of these oils may amount to 20 per cent. Sesame oil seems to be the least allergenic. Induration, itching, bleb formation and swelling of the neighboring tissues may be slight after the first or second injection, but they may become increasingly severe and may cause significant disability and pain for relatively long periods of time. Occasionally a patient will respond to the first injection with a severe reaction. Sevringhaus has pointed out repeatedly the need for a medium other than oil.

We have already reported our employing injections of estrone crystals suspended in aqueous medium in order to obtain freedom from allergic reactions (1). This preparation, now available commercially, has proven satisfactory not only from this standpoint, but also because of its increased effectiveness over estrone dissolved in oil. This increased effectiveness is probably due to a slower rate of absorption of the estrone crystals from the site of injection, since, following the rapid absorption of the aqueous vehicle, the crystals of estrone behave like small implants which are more slowly absorbed from the tissues than the oil solution. We have therefore extended our experiments with aqueous suspensions of fat soluble hormones to another commonly used estrogen, diethylstilbestrol.

This well known synthetic estrogen is potent and inexpensive. Its usefulness is however curtailed because it induces a relatively high incidence of side reactions such as nausea, vomiting, dizziness, *etc.*, and this occurs when the material is administered by injections as well as by mouth. We have shown that this high incidence of unpleasant reactions is due to its rapid absorption into the blood stream, and that these toxic symptoms are the result of physiologic changes in the tissue, much like those which occur in early pregnancy where the symptoms are similar. When the absorption

Received for publication March 11, 1946.

into the blood stream is delayed by combining diethylstilbestrol with fatty acid esters such as propionic and palmitic acid, the incidence of these disagreeable reactions decreases (3). If it could be demonstrated that the aqueous suspension of diethylstilbestrol has likewise a slower absorption than that dissolved in oil, we would then have the advantages of decrease in toxicity, improved therapeutic action and freedom from the allergic reaction of the oil vehicle.

METHODS AND RESULTS

Two groups of menopausal women with typical symptoms of a moderate to a severe degree received by injection the preparation of diethylstilbestrol suspended in water. The injections were administered every two weeks and the doses were 2.5 mg. and 5 mg. The degree of relief from the symptoms was evaluated as three plus for excellent relief; two plus, moderate relief; one plus, slight relief; and 0, no relief. The use of menopausal patients for testing the potency of the following estrogens has already been described by us: estrone in aqueous suspension (1), diethylstilbestrol and its esters (3), estrone sulphate (4), hexestrol (2) and benzestrol (5).

THERAPEUTIC EFFECT ON MENOPAUSAL SYNDROME OF DIETHYLSTILBESTROL IN AQUEOUS SUSPENSION ADMINISTERED AT TWO WEEKS' INTERVALS

2.5 mg.		5 mg.	
No. of patients	Degree of relief	No. of patients	Degree of relief
36	+++	28	+++
64	++	20	++
6	+	3	+
5	0	2	0
101		53	

From the above tables it can be noted that diethylstilbestrol in aqueous suspension controls satisfactorily menopausal symptoms in the majority of women when injected at the relatively infrequent interval of every two weeks. The relief of these patients is similar to that obtained from the use of most of the commonly accepted estrogens, including the natural ones. The incidence of side reactions in the above series of cases were as follows: four of the 101 patients who received the 2.5 mg. dosage complained of nausea for from one to two days, and two of the 53 patients who received the 5 mg. dosage had similar symptoms over a similar period of time. The intensity of these reactions was not as severe, however, as that of many patients who have taken 1 mg. of diethylstilbestrol orally for only a few days.

This incidence of toxicity is considerably less than that demonstrated by patients who have received diethylstilbestrol in oil, as shown by the fact that 15 out of 32 patients who received 5 mg. of diethylstilbestrol in oil developed the severe nausea, vomiting, *etc.* (5). This would indicate that the absorption of crystals of diethylstilbestrol in aqueous medium is sufficiently delayed to prevent the sudden rise of blood estrogen which is responsible for the development of the untoward symptoms. While no claims are made here as to the greater potency of the material when placed in aqueous suspension, the fact that there is an increased effectiveness wherever this material is treated to delay its absorption, would indicate that its potency might be appreciably increased. Certainly we have little hesitation in using the aqueous suspension when compared with the trepidation felt upon administering the same material in oil. In addition to the increased usefulness of diethylstilbestrol when it is administered in the aqueous suspension for therapeutic purposes, its freedom from local allergic reactions, encountered rather frequently with the oil solutions, gives it an added value. Physicians should find this new dosage form a probably more effective preparation than that which is in use in the form of the oil solutions, but definitely safer from the standpoint of systemic toxicity and local irritation.

SUMMARY

1. Diethylstilbestrol in aqueous suspension is a satisfactory estrogen when administered to menopausal patients.

2. It induces a relatively low incidence of unpleasant reactions such as nausea, vomiting, *etc.*

3. This preparation possesses the further advantage of being free from substances that induce the local allergic reactions encountered with oil solutions.

The preparation of diethylstilbestrol crystals in aqueous suspension was furnished by Abbott Laboratories, North Chicago, Illinois.

REFERENCES

1. FREED, S. C. and J. P. GREENHILL. Therapeutic use of estrone suspensions. *J. Clin. Endocrinol. 1:* 983 (Dec. 1941).
2. FREED. S. C. Estrogen assay in the human. *Essays in biology,* Univ. of Calif. Press, 1943, pp. 193.
3. FREED, S. C., W. M. EISIN and J. P. GREENHILL. The therapeutic efficiency of diethylstilbestrol esters *J.A.M.A. 119:* 1412 (Aug. 22, 1942).
4. FREED, S. C., W. M. EISIN, and J. P. GREENHILL. Therapeutic effectiveness of estrone sulfate (conjugated equine estrogens). *J. Clin. Endocrinol. 3:* 122 (Mar. 1943).
5. FREED, S. C., W. M. EISIN and J. P. GREENHILL. Assay in the human female of synthetic estrogen, 118B. *J. Clin. endocrinol. 2:* 213 (Apr. 1942).

TESTOSTERONE PELLET IMPLANTATION

JOSEPH EIDELSBERG, M.D.

From the Endocrine Clinic, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University

TESTOSTERONE has found a definite place in the treatment of certain human diseases and syndromes. Although its value has been widely discussed and debated, it is nevertheless a specific therapy in conditions such as eunuchoidism and hypogonadism. The preparations and modes of administration vary—testosterone in oil by injection, methyl testosterone by mouth or sub-lingually, testosterone in cream by inunction, and so on. A previous paper (1) dealt with the implantation of testosterone pellets[1] as a method of administration. At that time a report was made of observations on 130 implants in 47 patients. Since then 52 more pellet implantations have been made, making a total of 182 in 61 patients. As proof of its practicability, efficacy, and desirability, this further report of two selected cases, who have received 19 and 12 implants respectively, is herewith presented.

Case 1

E. W. presented himself at the age of 32 years on January 23, 1941. He was a typical eunuch with the classical symptoms and signs. At an early age he had become aware of his hypogonadism (infantile penis, absence of testes, failure of facial hair to appear, scant axillary and supra-pubic hair, *etc.*). At the age of 26 years he had been treated with pituitary hormone preparations, and, later, with testosterone propionate in doses ranging from 2.5 mg. to 50 mg. at intervals of from two to seven days. The response had encouraged him to continue therapy, but he had frequently neglected treatment. The first implant was made on January 30, 1941 and the dates of the subsequent implants are as follows: no. 2, March 31, 1941; no. 3, August 18, 1941; no. 4, December 24, 1941; no. 5, March 14, 1942; no. 6, June 6, 1942; No. 7, September 8, 1942; no. 8, December 1, 1942; no. 9, February 25, 1943; no. 10, May 24, 1943; no. 11, August 25, 1943; no. 12, November 19, 1943; no. 13, February 11, 1944; no. 14, May 5, 1944; no. 15, July 28, 1944; no. 16, October 23, 1944; no. 17, January 16, 1945; no. 18, April 4, 1945; and no. 19, September 4, 1945. The total is nineteen to date. He now shaves every other day, erections are frequent, the penis has grown to normal adult size, and body hair is normal. He has become happy, contented, and masculine, and his only concern is whether the pellets will continue to be available.

Case 2

D. K. T. first appeared on October 13, 1941, aged 23 years. His complaints were "failure to develop as a male," first recognized at the age of ten years. He was a classical example of eunuchoidism. At the age of eight years and also at 12 years he was circum-

Received for publication January 16, 1946.

[1] The testosterone pellets were supplied by the Schering Corporation through Dr. Max Gilbert.

cised, but on presentation his penis measured about 1 cm. About four years ago he had received his first implant on November 1, 1941, and, subsequently, no. 2, on February 7, 1942; no. 3, May 23, 1942; no. 4, September 5, 1942; no. 5, January 26, 1943; no. 6, May 11, 1943; no. 7, September 24, 1943; no. 8, February 1, 1944; no. 9, June 22, 1944; no. 10, November 7, 1944; no. 11, March 27, 1945; and no. 12, August 22, 1945. The total is 12 to date. He has been married since June, 1943. He shaves once a week; erections are frequent; the penis (erect) is 9.2 cm. ($3\frac{3}{4}$ inches) in length; body, axillary, and suprapubic hair are fair in amount; he cohabitates regularly and satisfactorily, and leads a normal adult life.

IMPLANTATION METHOD

The first implants were made with the original trocar (1). Since then the new bevel-edged trocar has been used. The posterior axillary area (right or left side) has remained the favorite site. Two to three cubic centimeters of two per cent procaine (with or without epinephrine 1-50,000) is infiltrated under the skin. The trocar is plunged through the skin at an acute angle, the inner plunger withdrawn, and three, 75 mg. pellets are introduced and pushed through with the rod. The trocar is then partially withdrawn and re-inserted at a slight angle and distance from the first three pellets, through the original puncture wound. Again three pellets are introduced. The trocar is then withdrawn, pressure made for a few minutes, to control the oozing or bleeding, which is usually very slight, and a simple dry dressing applied. After five or six days this is removed and invariably the wound is found perfectly healed. After two months the site of implantation is hardly recognizable.

EFFECTS AND RESULTS

Following regularly repeated implantations a more or less continuous flow of testosterone to the body probably occurred as judged by the reports of the patients. The clinical response has been maintained, both subjectively and objectively. Determinations of 24-hour urine 17-ketosteroids at intervals have consistently shown the amounts excreted in 24 hours to vary from 12.1 mg. to 19.5 mg. The excretion for the two patients reported above was 5.3 mg. and 8.4 mg. before therapy was begun, and varied from 12.8 mg. to 19.1 mg. in the years following the onset of treatment. When re-implantation was made regularly (three to four months), a "decline" or subsidence of testosterone effects did not occur. The metabolic effects of testosterone, such as retention of nitrogen, sodium, water, *etc.*, have been maintained (2).

The dosage is not left to the patient. There is not the possibility of omission of therapy. Frequently repeated injections are made unnecessary. The patient is kept under medical observation and supervision. Occasionally a pellet has been extruded. Infection did not occur. The procedure has been found simple, safe, painless, and satisfactory. The dose has been six,

75 mg. pellets inserted as described. The implantation scars are barely recognizable after a few months. A number of patients, who had tried the various forms of administration, expressed a preference for the implantation method.

REFERENCES

1. EIDELSBERG, J. and E. ORNSTEIN. Observations on the implantation of testosterone pellets. *J.A.M.A. 117:* 1068 (Sept. 27, 1941).
2. EIDELSBERG, J., M. BRUGER and M. LIPKIN. Some metabolic effects of testosterone implants. *J. Clin. Endocrinol. 2:* 329 (May, 1942).

A CASE OF PRIMARY AMENORRHEA

GRETE STOHR, M.D.

From the Endocrine Clinic of the Woman's Hospital in the State of New York

THE therapeutic approach to primary amenorrhea due to pituitary or ovarian failure constituted one of the most unyielding problems among gynecologic endocrine disorders until the isolation and synthesis of the female sex hormones made available potent preparations for effective replacement therapy. Since clinical results with hormonal treatment have been described in a limited number of cases only, a report of further experiences along these lines seems warranted. Moreover, the case to be presented seems of particular interest, as uterine bleeding from a secretory endometrium was obtained both by parenteral and by oral therapy. Similar effects recorded in the literature were accomplished in secondary amenorrhea. In primary amenorrhea, Finkler (1) described bleeding from an endometrium "suggestive of a secretory phase" following cyclic hormonal treatment by the parenteral route only.

CASE REPORT

H. L., aged 22, presented herself with the chief complaint of never having menstruated. Her past history and that of her family were unessential. She was of German-Jewish extraction, the elder of two sisters; the younger sister was normally developed, married, and the mother of a healthy infant. The patient was emotionally undisturbed by her developmental abnormality.

PHYSICAL EXAMINATION

Patient was younger in appearance than her age, with pleasant feminine features. She was 157 cm. tall, with a high waistline, the lower measurements exceeding the upper ones. The span was 6.5 cm. longer than the height. The body contours showed feminine lines; in spite of general slenderness, there was pronounced obesity of the waistline and hips. The extremities were well shaped and the fingers did not show marked tapering. The breasts were flat cushion-like elevations and the mamillae were not developed; breast tissue was not palpable. There was no pubic hair, but a few axillary hairs were present. (Fig. 1A, 1B). The external genitalia were greatly underdeveloped, the labia minora forming thin folds and the labia majora low elevations. The hymen was intact and delicate. The vagina was short but of normal diameter. Palpation revealed the uterus to be small and in normal position; the vaginal portion was exceedingly small but of typical appearance. The corpus-cervix ratio was of the adult type.

THERAPY

A diagnosis of hypo-ovarianism with hypogenitalism and primary amenorrhea was made and substitutional therapy instituted. This may be divided into four phases as shown below.

Received for publication February 19, 1946.

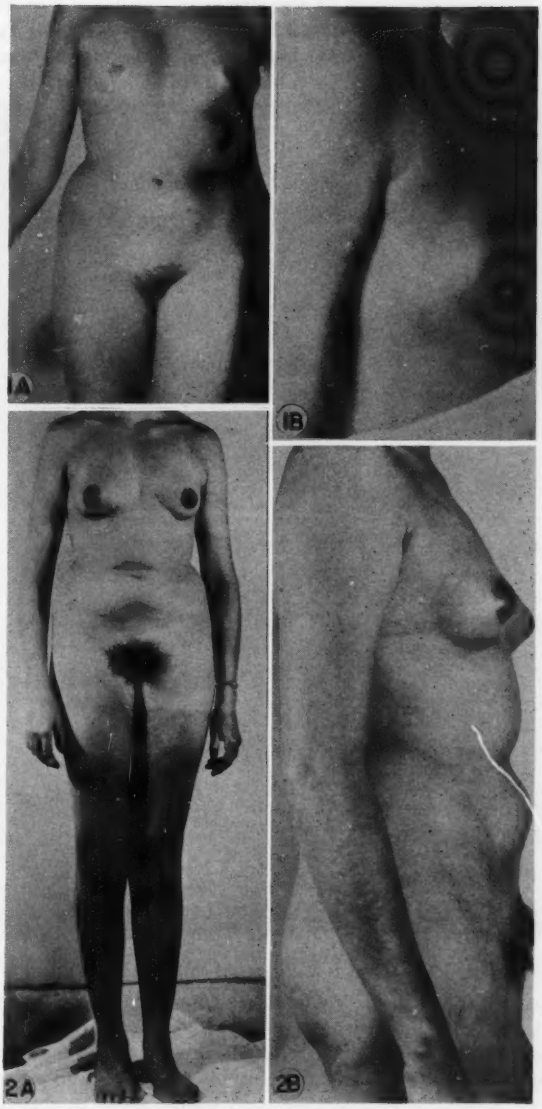


FIG. 1A. Patient, *H.L.*, aged 22; photograph showing marked hypogenitalism before institution of hormonal therapy.

FIG. 1B. Lateral view of patient, *H.L.* This photograph was taken at the same time as Figure 1A.

FIG. 2A. Anterior view of patient, *H.L.* after six months of hormonal therapy. Note development of breasts and of pubic hair.

FIG. 2B. Lateral view of patient, *H.L.* This photograph was taken at the same time as Figure 2A.

First phase. The implantation of 72 mg. estrone in two doses given two weeks apart resulted in gradual mammary growth and in the appearance of pubic hair and increase of axillary hair. Yet, no obvious development of the external or internal genitalia oc-

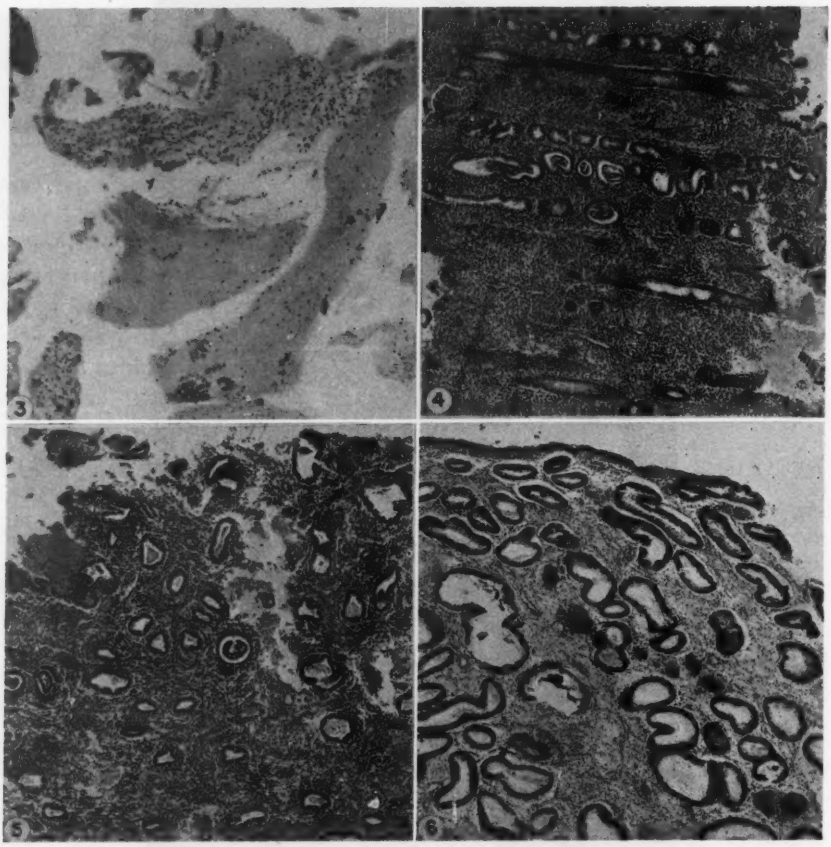


FIG. 3. Biopsy, March 7, 1941. A few epithelial cells in blood; no endometrial mucosa.

FIG. 4. Biopsy, May 24, 1941. Proliferative endometrium following intensive parenteral treatment with estradiol benzoate.

FIG. 5. Biopsy, June 30, 1941. Early secretory endometrium produced by several courses of parenteral cyclic treatment with estradiol benzoate and progesterone.

FIG. 6. Biopsy, November 16, 1941. Secretory endometrium produced by oral replacement therapy with estradiol and pregneninolone.

curred during a period of three months. There were no bleeding episodes, but the emotional life of the patient exhibited marked changes, inasmuch as she began to lead an active dream-life focussed on sexual motives.

The vaginal smear which originally presented a high degree of atrophy showed 30

per cent cornification one month after initiation of therapy followed by a gradual return to the pretreatment status. Biopsies were attempted four weeks and three months after the first implantation, but in neither case could endometrial tissue be obtained (Fig. 3).

Second phase. The implants having been completely absorbed during the preceding three months, the patient was given five courses of cyclic intrasmucular injections of estradiol benzoate and progesterone within four and one-half months. It was intended to follow in general a dosage plan consisting of a total of 50,000 R.U. of estrogenic hormone during the first half, and of a total of 50 mg. of corpus luteum hormone combined with some estrogenic medication during the second half of the hypothetic cycle. However, certain deviations from this plan became advisable when bleeding occurred before termination of a given course of therapy and, furthermore, when the large doses of estrogens administered had brought about such marked developmental changes as to give the patient in every respect the appearance of a normally built mature woman (Fig. 2A, 2B).

Every such course of therapy induced bleeding lasting from three to five days. Repeated biopsy studies, at the end of the estrogenic phases of treatment, always revealed active proliferation. Fig. 4 shows the endometrial pattern of a specimen obtained during the third course of treatment when patient was transferred from estrogenic to progestogenic therapy. Early secretory activity (Fig. 5) was apparent in the specimen obtained at the end of the fourth course of treatment, following administration of a total of 50 mg. of progesterone in five divided doses over a period of one week. However, at the end of another full course of cyclic therapy the endometrium did not reveal progestational changes. Interruption of hormone administration for several weeks was accompanied by return of an atrophic endometrium.

Third phase. In order to determine whether oral medication also would elicit bleeding from a secretory endometrium a state of hormonal depletion was induced by withholding treatment for six weeks and by then instituting oral therapy. This consisted of five courses of cyclic treatment with estradiol and pregneninolone over a period of 14 months. The total amounts of estradiol administered during the first phases of the hypothetic cycles were 24, 48, 10, 10, and 10 mg. spread over 12, 12, 5, 10, and 10 days respectively. After such priming, the progestogenic hormone was given either alone or in combination with estradiol. The total amounts of pregneninolone were 500, 1000, 350, 420, and 750 mg. spread over 10, 10, 5, 6, and 5 days respectively. There was uterine bleeding four times during these five courses of oral therapy. Secretory activity of the endometrium (Fig. 6) resulted after the patient had received 1000 mg. of pregneninolone (second course of treatment). Similar results were obtained following 750 mg. of pregneninolone (fifth course of treatment), but no progestational changes occurred following smaller doses. Seemingly it matters little whether the amount of pregneninolone required is spread over 5 or 10 days. Table 1 gives the details of these three phases of treatment.

Fourth phase. During the following years therapy was of necessity irregular, and was dependent upon the free hormone supplies available for the indigent patient. During this period the results as evidenced by endometrial biopsies reflected exactly the amounts and types of hormones administered. In general a lower dosage was required for maintenance therapy than for stimulation of developmental changes.

The patient, now 27 years of age, reports sporadically to the clinic. She is able to maintain physical and mental equilibrium by periodical intake of various artificial estrogenic preparations. Female characteristics remain well developed; bleeding occurs from two to three times a year and she has become reconciled to a physical deficiency which, however, is no longer readily apparent.

TABLE 1

Date	Estrogenic therapy	Progestogenic therapy	Bleeding episodes	Endometrial biopsies
		First Phase		
12/14/40	Implant: 20 mg. estrone crystals			
12/21/40	Implant: 52 mg. estrone pellets			
1/18/41				No tissue obtained.
3/7/41				No tissue obtained.
		Second Phase		
3/17/41	1.67 mg. E.B.			
3/19/41	1.67 mg. E.B.			
3/21/41	1.67 mg. E.B.			
3/24/41	1.67 mg. E.B.			
3/31/41	1.67 mg. E.B.			
4/2/41		10 mg. P.		
4/5/41	1.67 mg. E.B.	10 mg. P.		Active proliferation.
4/7/41		10 mg. P.		
4/9/41		10 mg. P.		
4/11/41		10 mg. P.	Bleeding 5 days.	
4/22/41	1.67 mg. E.B.			
4/26/41	1.67 mg. E.B.			
4/28/41	1.67 mg. E.B.			
4/30/41	1.67 mg. E.B.			
5/3/41	1.67 mg. E.B.			
5/5/41	1.67 mg. E.B.			
5/6/41				Full proliferation.
5/7/41		10 mg. P.		
5/9/41			Bleeding.	
5/10/41		10 mg. P.		
5/12/41	1 mg. E.B.			
5/14/41	1 mg. E.B.			
5/17/41	1 mg. E.B.			
5/19/41	1 mg. E.B.			
5/21/41	1 mg. E.B.			
5/23/41	0.33 mg. E.B.			
5/24/41		10 mg. P.		Excellent proliferation.
5/26/41		10 mg. P.	Spotting.	
5/28/41	1 mg. E.B.	10 mg. P.	Bleeding several days.	
5/29/41	1 mg. E.B.	10 mg. P.		
6/13/41				Atrophy.
6/14/41	1 mg. E.B.			
6/16/41	1 mg. E.B.			
6/18/41	1 mg. E.B.			
6/20/41	1 mg. E.B.			

TABLE I (Cont'd.)

Date	Estrogenic therapy	Progestogenic therapy	Bleeding episodes	Endometrial biopsies
		Second Phase (cont'd)		
6/24/41		10 mg. P.	Bleeding few hours.	Proliferation.
6/25/41		10 mg. P.		
6/26/41		10 mg. P.		
6/28/41	0.33 mg. E.B.	10 mg. P.		
6/30/41		10 mg. P.		
7/1/41			Bleeding 5 days.	Early secretion.
7/7/41	0.33 mg. E.B.			
7/11/41	0.33 mg. E.B.			
7/14/41	0.33 mg. E.B.	10 mg. P.		
7/19/41	0.33 mg. E.B.	10 mg. P.		Proliferation.
7/21/41		20 mg. P.		
7/24/41	0.33 mg. E.B.	10 mg. P.		
7/26/41		10 mg. P.		No secretion.
7/30/41			Bleeding 3 days.	
		Third Phase		
9/11/41 to 9/22/41	2 mg. E. daily			Atrophy (9/11/41) Proliferation (9/22/41)
9/23/41 to 10/2/41		50 mg. Po. daily	Bleeding 6 days.	
10/8/41				Hypoplasia.
10/26/41 to 11/6/41	4 mg. E. daily			
11/7/41 to 11/16/41	0.4 mg. E. daily	100 mg. Po. daily	Bleeding.	Secretion (11/16/41)
6/15/42	0.33 mg. E.B.			
6/17/42	0.33 mg. E.B.			
6/19/42	0.33 mg. E.B.			
6/22/42	0.33 mg. E.B.			
6/24/42	0.33 mg. E.B.			
6/26/42	0.33 mg. E.B.			
6/29/42		10 mg. P.		
6/30/42		10 mg. P.		
7/1/42		10 mg. P.		
7/3/42		10 mg. P.		
7/6/42				Secretion.
7/7/42			Bleeding 5 days.	

TABLE I (Cont'd.)

Date	Estrogenic therapy	Progestogenic therapy	Bleeding episodes	Endometrial biopsies
		Third Phase (cont'd)		
8/25/42 to 8/29/42	2 mg. E. daily			
8/30/42 to 9/3/42		70 mg. Po. daily		
9/4/42				Atrophy.
9/26/42 to 10/5/42	1 mg. E.			Hyperproliferation.
10/6/42 to 10/11/42	0.4 mg. E.	70 mg. Po.	Staining 5 days.	Atrophic endometrium.
10/21/42 to 10/30/42	1 mg. E.			
10/31/42 to 11/4/42	0.4 mg. E.	150 mg. Po.		Secretory endometrium.
11/6/42			Bleeding 3 days.	

KEY:
E.B. = Estradiol Benzoate
E. = Estradiol
P. = Progesterone
Po. = Pregneninolone

Schedule of treatment of patient H. L. during a 2-year period. Endometrial response to therapy and bleeding episodes.

DISCUSSION

Other workers have found pituitary gonadotrophic substances of no avail in inducing normal ovarian function in patients with primary amenorrhea. However, there are on record cases in which feminization including bleeding from a secretory endometrium was attained by cyclic replacement therapy consisting of the parenteral administration of gonadal hormones.

In the case presented, exhibiting extreme hypogenitalism and primary amenorrhea, implantation of 72 mg. of estrone initiated the development of secondary sex characteristics but was ineffectual in developing the endometrium and in producing uterine bleeding. However, cyclic therapy with estrogenic and progestogenic hormones administered parenterally or orally

caused proliferation and secretory changes in the endometrial mucosa indistinguishable from those elicited by the hormonal stimuli of normally functioning ovaries. Bleeding occurred repeatedly but could be produced from a progestational endometrium only if the optimal quantitative estrogen-progestogen relation had been established. If oral medication was applied, a minimum of from 750 to 1000 mg. of pregneninolone was required to obtain secretory activity after adequate priming with estradiol. Other investigators had demonstrated that similar quantities of pregneninolone were needed to produce comparable results in surgical castrates and postmenopausal women. For instance, Neustaedter (2) demonstrated that from 900 to 1200 mg. of pregneninolone caused secretory changes in the endometria of six surgical castrates. Birnberg and his group (4) showed that from 1000 to 1200 mg. pregneninolone brought about progestational endometria in four out of six postmenopausal women. In a previous communication (3) the author demonstrated that secretory activity was restored in a case of anovulatory bleeding by two courses of pregneninolone therapy, each of 1000 mg. Thus it seems that if the ovaries are absent or non-functioning, from 750 to 1200 mg. of the orally active corpus luteum preparation will produce endometrial changes identical with those occurring in women of the reproductive age group during the second half of the cycle.

The foregoing case history illustrates what may be expected from oral estrogenic and progestogenic therapy in patients of a similar type.

The estradiol (*Dimenformon*), estradiol benzoate (*Dimenformon Benzoate*), progesterone (*Progestin*), and pregneninolone (*Progestoral*) used in this study were supplied by Roche-Organon, Inc., Nutley, New Jersey, by the courtesy of Dr. Leo A. Pirk.

REFERENCES

1. Finkler, R. S., and R. D. Bass. Primary amenorrhea (Report of 21 Cases). *M. Woman's J. 47:* 3 (January, 1940).
2. Neustaedter, T. The effect of oral administration of alpha estradiol and pregneninolone upon the human castrate uterus. *Am. J. Obst. & Gynec. 42:* 86–92 (July, 1941).
3. Stohr, G. Oral hormone therapy in anovulatory bleeding. *J. Clin. Endocrinol. 2:* 633–635 (November, 1942).
4. Weber, H. W., L. Kurzrok, and C. H. Birnberg. Effect of inunction of alpha estradiol and of oral medication with pregneninolone upon post-menopausal human uterus. *J. Clin. Endocrinol. 2:* 392–394 (June, 1942).

THE XENOPUS TEST IN TUMOUR OF THE TESTIS

D. R. MEIRING, M.B., CH.B.,
AND
H. ZWARENSTEIN, D.Sc.

From the Departments of Pathology and Physiology, University of Cape Town

ZONDEK, in 1929, employing immature female mice as in the diagnosis of pregnancy, first demonstrated the presence of gonadotrophic hormone in the urine of a man suffering from a teratoma of the testis. In 1930 Heidrich, Fels and Mathias (3) reported a similar observation in a case of chorionepithelioma of the testis. In this case the excretion of the hormone exceeded the remarkable figure of 50,000 "mouse units" per litre of urine. Ferguson (2) advocated bio-assay of the urine for gonadotrophic hormone not only as an aid to diagnosis, but as a guide to the prognosis and radiosensitivity of testicular tumours.

In 1933 Shapiro and Zwarenstein (9) described a test for pregnancy using the South African clawed frog, *Xenopus laevis*. Zwarenstein and Duncan (12), reviewing ten years' experience of the test, described a dilution test for the rough quantitative estimation of gonadotrophic hormone in those cases where the amount excreted was unduly large. The dilution test has proved of considerable value in the diagnosis of hydatidiform mole and chorionepithelioma in the female.

The Zenopus test has also been employed in the investigation of cases of suspected testicular tumours. Some of these proved on histological examination to be chronic inflammatory affections of the testis or epididymis, and in these the test was consistently negative. The remainder, with one exception where there was no histological control and which gave a negative test, are briefly compared in the following table:

Case	*Age*	*Clinical diagnosis*	*Xenopus test*	*Histological diagnosis*
1	41	Testicular tumour	Negative	Seminoma
2	34	Hydrocele	Not done	Embryonal adenocarcinoma
		Readmitted after 3 months; ?secondary deposits; clinical examination negative.	Positive	No autopsy obtained.
3	41	?Testicular tumour	Negative on neat urine	Teratoma containing a mixture of tissues
		Re-admitted after 2 years; secondary deposits in para-aortic glands.	Positive	Chorionepithelioma

4	29	?Testicular tumour	Negative	Seminoma
5	37	Hydrocele + underlying pathology of testis or epididymis	Negative	Embryonal adenocarcinoma
6	50	Testicular tumour	Negative	Melanoma (Secondary deposit)

Cases 2 and *3*, in which positive Xenopus tests were obtained, are worth recording in some detail.

Case 2: A. v. W., a coloured, male, printer's assistant, aged 34 years, was admitted to the hospital in May, 1936, for "hydrocele." A left orchidectomy was performed, and he was discharged apparently well three weeks later. No Xenopus test was performed during this admission. The histological features of the specimen removed at operation were those of a very cellular tumour of the testis, the cells being much less uniform in type than in the common seminoma, and in parts tending to form imperfect acini *i.e.* an embryonal adenocarcinoma.

The patient was re-admitted three months after his discharge, complaining of pain in the left loin and left iliac fossa for seven weeks. His general condition was described as good, and there was no clinical evidence of a local recurrence or of glandular or visceral metastases. The Xenopus test, however, was positive.

The patient left the hospital and was confined to his bed until his death five months later. During the latter half of this period he developed paralysis of the lower half of his body. No autopsy was obtained.

Case 3: A.S., a European, aged 43, was admitted to the hospital in November 1942 complaining of swelling of the right testis for seven months and tenderness of the nipples for three months. Orchidectomy was performed for a suspected tumour of the right testis. A Xenopus test done on neat urine at this time was negative. No further specimen was submitted for examination, and the patient was discharged apparently fit. The histological appearance of the tumour removed was that of a teratoma showing differentiation into cartilage, muscle, glandular acini, squamous epithelium and myxomatous tissue. In addition there were small, more cellular areas of epithelial tissue, suggesting more active growth.

Two years later the patient returned to hospital complaining of pain in the back and tender swelling of the breasts. Examination revealed gynaecomastia and a hard mass in the epigastrium, presumably metastases in the para-aortic lymph glands. Accordingly he was given a course of deep x-ray therapy to the epigastrium.

Six weeks later he was admitted for excision of the left testis, a procedure prompted by the favourable results following castration reported by Saleeby (8). It was found that the epigastric mass was no longer palpable, and the patient appeared thin but subjectively well. Gynaecomastia was, however, still present and the urine gave a positive Xenopus test. The dilution test was negative.

After his discharge from the hospital the patient's condition rapidly deteriorated. Further Xenopus tests were positive but the dilution test remained negative. He complained particularly of a sick feeling in the epigastrium, and despite further x-ray therapy, became emaciated, cachectic, and died in February, 1945.

At post-mortem the liver was found greatly enlarged (3300 gm.), and contained numerous deposits of reddish-yellow tumour tissue. The abdominal lymphatic glands were extensively invaded, and metastases were found also in the lungs, pancreas and adrenal glands. The adrenals were completely destroyed and replaced by tumour tissue. A portion of this was ground up with sand, and the extract obtained was injected into

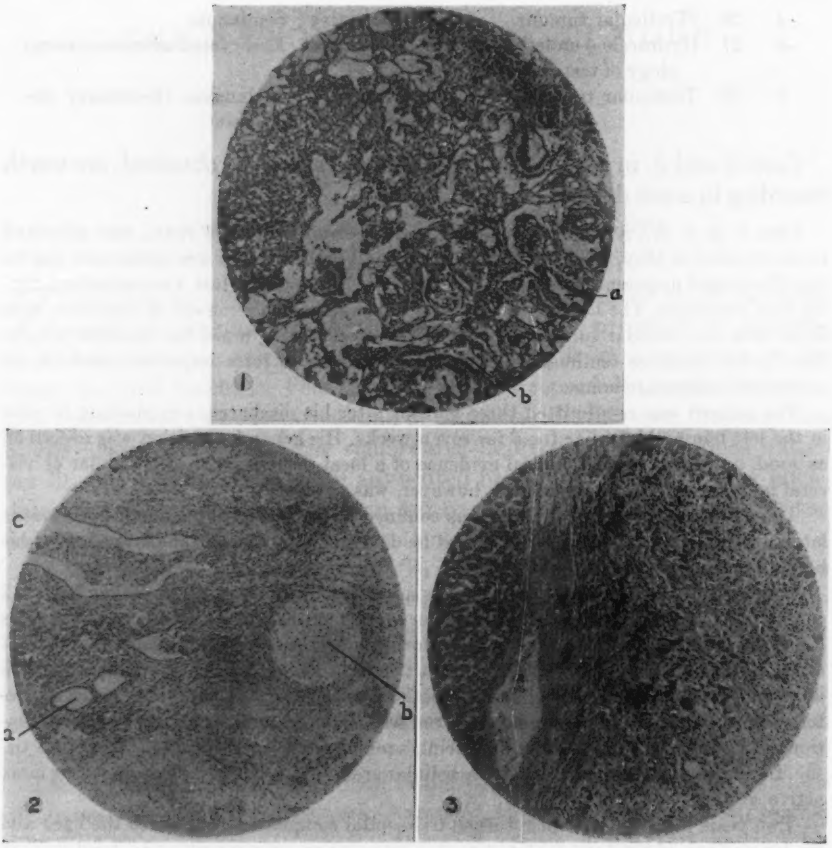


FIG. 1: Section of embryonal adenocarcinoma (×100). The cells vary much in appearance and show a tendency to be grouped in acini as at (a) and (b).

FIG. 2: Section of teratoma containing a mixture of tissues (×100): (a) gland acini, (b) cartilage, (c) cyst lined by flattened epithelium.

FIG. 3. Microphotograph showing invasion of liver tissue by chorionepithelioma (×100).

frogs as in the routine pregnancy test. Ovulation occurred, indicating the presence of a gonadotrophic substance. A control test with normal adrenal tissue gave a negative result.

Histological examination of the organs removed at autopsy showed very extensive invasion by tumour tissue, the structure being that of a chorionepithelioma.

The breasts showed typical gynaecomastia.

DISCUSSION

Using the "mouse test," Zondek (11) found that while the luteinizing reaction (dependent on chorionic gonadotrophin) occurred in relatively few (three out of 14) cases of testicular tumour, a follicle-stimulating reaction was obtained much more frequently, and could occur even in non-neoplastic disease of the testis. Here it was apparently due to overaction of the pituitary consequent in the destruction of one testis.

Ferguson (2) maintained that the hormone output of testicular tumours could be closely correlated with their histological structure, so that a fairly accurate diagnosis could be made from a bio-assay of the urine. The hormone content was highest in chorionepithelioma, lowest in the "adult" mixed teratoma, while embryonal carcinoma and seminoma occupied intermediary positions. He recorded his results in units of "Prolan A" without differentiating between follicle-stimulating and luteinizing hormone.

Others, however, believed such a distinction to be of value, and Montpellier and Herland in 1933, and Seror in 1935 [quoted by McDonald (6)], were of the opinion that a seminoma could be differentiated from a chorionepithelioma by means of the Aschheim-Zondek reaction. Urine from a case of chorionepithelioma contained chorionic gonadotrophin and gave the complete reaction with the formation of corpora lutea, while with seminoma only follicular maturation occurred.

Hamburger [quoted by Twombley *et al.* (10)] went further and considered that chorionic gonadotrophin occurred in the urine of patients with chorionepithelioma and adenocarcinoma, while in cases of seminoma (including embryonal carcinoma with or without lymphoid stroma) follicle-stimulating hormone only was found.

The belief that chorionic gonadotrophin is not found exclusively in cases of chorionepithelioma is supported by Twombley *et al.* (10). These authors, however, disagree with Hamburger and contend that both types of gonadotrophic hormone are found in each group of patients. Occasionally they occur together but one usually predominates. From an analysis of a large number of cases these authors conclude that there is little correlation between the histological structure of testicular tumours and the type and quantity of hormone excreted in the urine, so that the histology of a tumour is not predictable from bio-assay of the urine alone.

In the face of such conflicting opinion it becomes difficult to assess the actual diagnostic value of bio-assay of urine in cases of suspected testicular tumour. Perhaps the confusion is in part due to the use, as test animals, of unhypophysectomised mice and rats, as Noble *et al.* (7) have shown that the test animal's own pituitary may considerably modify the effects of injected gonadotrophic substances. The difficulty is circumvented by the

use of *Xenopus laevis* for the test. In this animal the presence of ovulation constitutes a positive result. Ovulation will occur if the extract of urine injected contains sufficient chorionic gonadotrophin, but if it contains only follicle-stimulating hormone the test will be negative.

Hitherto, only two cases of testicular tumour have shown a positive Xenopus test. In one of these (*Case 3*) there was a widely disseminated chorionepithelioma, but in *Case 2* the nature of the tumour at the time of the test was not known. The primary growth in *Case 2* was an embryonal adenocarcinoma but no test was done until three months after its removal. The positive result then obtained was the first definite indication of the presence of metastases. Unfortunately their histological structure was never ascertained as there was no autopsy.

The Xenopus test has, therefore, not yet shown whether chorionic gonadotrophin may occur in the urine of cases of testicular tumour other than chorionepithelioma. Pending further experience it may be concluded that the test is of rather limited diagnostic value, but inasmuch as it may disclose the presence of chorionic tissue it should form part of the investigation of all cases of suspected testicular neoplasm, and may be of considerable value in the early detection of secondary or metastatic tumour growth after orchidectomy.

Prognosis and radiosensitivity

Ferguson (2) found that in the majority of his cases there was a reduction in the excretion of gonadotrophic hormone in the urine after irradiation of the primary tumour or its metastases. Thus, he considered that repeated bio-assay of the urine supplied a good index of the radiosensitivity of tumours of the testis, and hence a valuable guide to prognosis.

Subsequent work has, however, only partly supported this view. In some cases [Beilly *et. al.* (1)] it has been possible fairly accurately to follow the clinical course by repeated quantitative estimation of the gonadotrophic hormone excreted in the urine. More often, however, the results have been disappointing. Hinman and Powell (4) concluded that such failure might be due to the likelihood of x-ray therapy inhibiting the ability of a tumour to produce gonadotrophic hormone without destroying the tumour. In one of our cases, *No. 3*, this might explain why, despite x-ray therapy, the malignant disease progressed to a fatal issue without there occurring a rise in hormone output sufficient to give a positive dilution test.

In a later publication, Hinman and Powell (5) expressed their conviction that while quantitative estimations of hormone output alone were unreliable indications of prognosis after irradiation, very helpful information

could be obtained by correlating the hormone output of a tumour with its histological structure, and grading it according to a hormonal-histological classification. This procedure, in their cases, proved of great value in determining prognosis and treatment.

Twombley *et al.* (10) (1942) are of the opinion that repeated hormonal tests are of little value in following the clinical course, and in most cases are not worth doing. They believe, however, that the test should be performed on all cases in order to determine whether the tumour is producing chorionic gonadotrophin, as this is a bad prognostic sign. They attach little prognostic significance to the presence in the urine of follicle-stimulating hormone.

In this respect the Xenopus test would be of considerable value. Unfortunately it has, as yet, found very limited application in the diagnosis and study of neoplasms of the testis. The results obtained, however, have conformed well with what could be expected on theoretical grounds, and it is hoped that it will more often be resorted to in the future.

SUMMARY

The Xenopus test has been performed in a series of cases of suspected testicular tumour, and a positive result was obtained in two of these.

The diagnostic and prognostic value of bio-assay of the urine in cases of tumour of the testis is discussed. It would seem that it is particularly desirable to ascertain whether or not chorionic gonadotrophin is being excreted, and for this purpose *Xenopus laevis* is an eminently suitable test animal.

ACKNOWLEDGEMENTS

We are indebted to Professor B. J. Ryrie for placing at our disposal the histological material of the Department of Pathology and to Mr. I. de Villiers for the preparation of the microphotographs.

REFERENCES

1. Beilly, J. S., I. Kurland and M. Jacobi. Hormone excretion and bioassay of extirpated tumor in teratoma of testis. *Endocrinology. 26:* 965–970 (1940).
2. Ferguson, R. S. Clinical evaluation of quantitative excretion of prolan A in teratoma testes. *J. Urol. 31:* 397–409 (1934).
3. Heidrich, L., E. Fels and E. Mathias. Testikuläres Chorionepitheliom mit Gynäkomastie und mit einigen Schwangerschaftscheinungen. Gleichzeitig ein Beitragzur Pathologie der hormonal-aktiven Gewächse. *Bietr. z. klin. Chir. 150:* 349–384 (1930).
4. Hinman, F. and T. O. Powell. Gonadotropic hormone in urine of men with tumor of testis. *J. Urol. 34:* 55–71 (1935).
5. Hinman, F. and T. O. Powell. Management of tumor of testicle. *J.A.M.A. 110:* 188–190 (1938).

6. McDonald, S., Jr. Observations on chorionepithelioma testis, with record of case. *Am. J. Cancer. 34:* 1–14 (1938)
7. Noble, R. L., I. W. Rowlands, M. H. Warwick and P. C. Williams. Comparative effects of certain gonadotrophic extracts on ovaries of normal and hypophysectomized rats. *J. Endocrinol. 1:* 22–35 (1939).
8. Saleeby, R. R. Teratoma of testicle; metastasis to epigastrium treated by bilateral orchidectomy—recovery. *Ann. Surg. 119:* 262–265 (1944).
9. Shapiro, H. A. and H. Zwarenstein. *Proc. Roy. Soc. S. Afr.* (October, 1933).
10. Twombley, G. H., H. M. Temple and A. L. Dean. Clinical value of Aschheim-Zondek test in diagnosis of testicular tumors. *J.A.M.A. 118:* 106–111 (1942).
11. Zondek, B. Maligne Hodentumoren und Hypophysenvorderlappenhormone. Hormonale Diagnostik aus Horn, Hydrocelenflüssigkeit und Tumorgewebe. *Klin. Wchnschr. 11:* 274–279 (1932).
12. Zwarenstein, H. and D. G. Duncan. Ten years of Xenopus pregnancy test. *Clin. Proc. 3:* 186–193 (1944).

Book Review

SHERF, DAVID and T. J. BOYD. *Clinical Electrocardiography*. Philadelphia, Pa., J. B. Lippincott Company, 1946, 267 pp., 2nd ed.

The book reviewed is an American edition, while two previous editions were published in England. There were editions in French, Spanish and Portuguese.

This book has many features which distinguish it from other textbooks on the subject. One is the fact that the authors are not dogmatic and do not assume the rôle of authoritative finality. This is a very healthy attitude toward electrocardiography. This is not merely a collection of tracings with explanatory remarks, but actually a text with illustrations. The many pitfalls and problems facing the present state of electrocardiography are discussed especially well in the chapters on "Bundle Branch Block" and "Chest Leads." Another useful feature of the book is the extensive list of references attached to each chapter; the space devoted to references in some chapters is greater than the text on the subject itself. The book is thus useful as a ready reference index for the student of the subject.

While the book is published neatly, the material is not always arranged in a palatable form. There is, for instance, a special chapter on the deep Q3. The significance of this abnormality, however, is discussed separately in the chapter on coronary thrombosis.

On the whole it is a very useful book to read and study after one has attained an elementary knowledge of the subject from the leading textbooks on cardiology.—*L.S.*

Abstracts of

CURRENT ENDOCRINE LITERATURE

Editor; D. A. McGINTY. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN JR., G. G. RUDOLPH, L. T. SAMUELS.

GONADS

BADENOCH, A. W. Descent of the testis in relation to temperature. *Brit. M. J. 2:* 601–603 (1945).

The author has studied the intrascrotal and peritoneal temperatures in twenty-five adults at the time of operation for inguinal hernia. The temperature was invariably lower in the scrotum than in the iliac fossa. The difference varied from 0.8° C. to 3.7° C. with an average difference of 2.2° C. The influence of temperature on spermatogenesis was reviewed.—*L.T.S.*

BURDICK, H. O. Further observations on induced ovulation in the mouse as a rapid test for pregnancy. *Am. J. Physiol. 145* (3): 387–390 (1946).

Mature albino mice of the Rockland strain weighing at least 20 gm. and having vaginal smears showing an abundance of leucocytes typical of diestrus were used as the basic test animal. Samples of morning urine were refrigerated without preservative. Single subcutaneous injections of untreated urine were made and autopsies performed 18 to 24 hours later. Ovulation is manifest by the distention of the ampulla of the oviduct with fluid and the egg mass, and can be seen with a dissecting microscope. The occurrence of ovulation is regarded as a definite end point of the test. The chorionic gonadotropin content of urines from pregnancies of six to eight weeks' duration contained from 10,000 to 80,000 mouse ovulating units per liter. The minimal ovulating doses of urine containing 10,000 mouse ovulating units per liter is 0.1 cc. There was usually a marked reduction in ovulating capacity by the third month of pregnancy. The potency of stored urine was maintained for approximately 30 days. It was found that pregnant mice could be used as test animals provided they were not injected within the first three days of pregnancy while the fertilized ova were still in the oviducts. Pregnant mice were slightly more responsive than diestrus mice.—*F.N.A.*

CALATRONI, C. J., V. RUIZ, AND G. DI PAOLA. Castration during pregnancy. *Obst. y ginec. latino-am. 3:* 145 (1945).

Fraenkel observed in rabbits that castration during pregnancy caused miscarriage.

The authors have examined the literature and analyzed the results in a series of 85 women who were surgically castrated during the first four months of pregnancy in order to determine whether miscarriage follows castration during pregnancy in women. The series included only patients to whom no morphine, progesterone or any other abortion-preventing medication had been given after the operation. Cases in whom only the corpus luteum or the ovary containing it was removed were not included in the analysis. Of the 85 cases studied, five were operated on during the first month of pregnancy, 29 during the second month, 27 during the third month, 20 during the fourth month, and four at an unspecified time during the first four months. Of these 85 cases, 65 (76.4 per cent) had a normal delivery, 13 (15.2 per cent) miscarried, 6 (7 per cent) were still pregnant at the time of the survey, and 1 (1.1 per cent) was delivered about 15 days before term. A study of the patients that miscarried showed that in three cases the mothers died three hours, 12 and 15 days, respectively, after the castrating operation, one of them with neoplastic metastases. The authors conclude that these three cases aborted because of the conditions which lead to their deaths rather than from the castration. Another case that presented symptoms of abortion was operated upon, and hence was excluded from the group. Hence, the number of miscarriages attributed to the loss of the corpus luteum is reduced to nine (10.5 per cent), a rate of miscarriage similar to that observed after any abdominal operation in pregnant women. The authors conclude that once the ovum is lodged in the uterus it does not need the corpus luteum, and hence excision of ovarian tumors during pregnancy should not be feared. The paper contains 127 references and five tables.—*J.R.R.-M.*

DAUGHTRY, D. C. Arrhenoblastoma. *Am. J. Obst. & Gynec. 50* (5): 539–541 (1945).

The author reported an instance of arrhenoblastoma in a 37 year old, married, nulliparous colored woman. Six months following surgical removal there was a marked decrease in masculine features.—*C.D.D.*

DAVIS, C. D. AND E. C. HAMBLEN. A comparative study of the clinical responses of women with hypofunctioing ovaries to two methods of combined gonadotropic therapy. *Am. J. Obst. & Gynec. 50* (3): 269–274 (1945).

Twenty-one patients with degrees of hypo-ovarianism varying from deficient sexual maturation to presumed ovarian sterility associated with bleeding from immature progestational endometrium, were subjected to two systems of gonadotropic therapy. The primary criterion for evaluation of the responses was a study of endometrial biopsies taken prior to and following treatment.

One method of therapy employed the single and sequential administration of equine and chorionic gonadotropins; the so-called one-two cycle gonadotropic therapy. The other method of therapy employed a preparation which contained a mixture of 'pituitary synergist' and chorionic gonadotropin, which had to be given daily from the fifth through the twenty-fourth days of the cycle in order to produce any positive responses.

The authors concluded that both types of therapy were effective in producing progestational endometriums in patients experiencing various grades of estrogenic bleeding but that the latter type of therapy yields a lower incidence of positive responses and a higher incidence of untoward reactions.—*C.D.D.*

EREZ, NASID. A case of Meig's syndrome. *J. Obst. & Gynaec. Brit. Emp. 52* (5): 506–509 (1945).

A case of Meig's syndrome reported from Istanbul showed ascites, right pleural effusion and a fibroma of the right ovary, the size of a foetal head. Recovery followed removal of the tumor. This is said to be the 42nd recorded case.—*R.A.C.*

EVERIDGE, J. Case of pseudohermaphroditism and adrenalism. *Proc. Roy. Soc. Med. 38:* 649 (1945).

The author reports a case of a 19-year-old patient whose sex could not be determined at birth. The individual was born with two teeth and walked and talked at nine months. Axillary and pubic hair appeared at the age of three years. Shaving was begun at nine and the voice changed at 12. At ten there was periodic abdominal pain and monthly discharge of blood from the urethra. From the age of 11 there was periodic swelling of the breasts. The patient was unusually bright, preferred masculine pursuits, and was a good athlete. There was no evidence of a sexual psychological problem. The 17-ketosteroids in urine were 75.7 mg. per 24 hours. Laparotomy revealed female genital organs and the uterus and one ovary were removed. There was no enlargement of the adrenals. The vagina opened into the urethra. No postoperative values on ketosteroids were given, and no description of the ultimate development of the external genitalia.—*R.C.*

FAULKNER, R. L. AND E. A. RIEMENSCHNEIDER. Reactivation of endometriosis by stilbestrol therapy. *Am. J. Obst. & Gynec. 50* (5): 560–561 (1945).

The authors reported a patient with severe periodic bleeding from endometriosis of the bowel which required in all over seventy partial or whole transfusions. Surgical castration was finally done and the patient had no more bleeding until given diethylstilbestrol for menopausal symptoms. This lead to a severe recurrence of bleeding. Permanent recovery followed discontinuance of this therapy.—*C.D.D.*

FRANK, I. L. Uterine bleeding and extragenital disturbances. *Am. J. M. Sc. 210:* 787 (1945).

In this review article the author analyzes 125 communications from the literature in terms of extragenital disturbances and diseases of the body that have been reported to be associated with uterine bleeding in order to estimate the frequency and importance of such causes. He discusses: 1) the influence of the central nervous system, 2) physical agents, 3) diseases of the endocrine glands, 4) infectious diseases, 5) allergy and the menstrual cycle, 6) blood dyscrasias, 7) avitaminosis, 8) visceral disease, and 9) atypical bleeding of physiologic origin. He concludes that the ultimate origin of very many cases of dysfunctional uterine bleeding is not sought out, because physicians have been willing to accept as causes either minor incidental pelvic lesions or endocrine imbalances, which may be merely intermediate effects. Relief following hormone therapy or curettage does not demonstrate a primary disease, and both may be followed by a recurrence of menorrhagia. Uterine bleeding has two dangerous implications: cancer and blood loss. The latter usually receives prompt therapy, but the former is insidious and cannot safely be kept waiting. Metrorrhagia usually means a neoplastic lesion of the uterine epithelia and demands an early diagnostic curettage. Menorrhagia, however, is almost always

benign. Tracing menorrhagia to an otherwise subclinical disturbance is a tedious and uncertain process, but on occasion it will suggest cures rather than palliatives, and may often avert unnecessary or fruitless surgical procedures. Accumulating data indicate that uterine bleeding commonly derives from systemic rather than purely local disturbances.—*E.C.R.,Jr.*

GILL, A. J., G. T. CALDWELL, AND J. L. GOFORTH. Choriocarcinoma of the testicle. *Am. J. M. Sc. 210:* 745 (1945).

The authors report the history and pathological findings of three recent cases of choriocarcinoma of the testicle. After histological study of these cases and consideration of part of the extensive literature on the subject, they believe that these tumors arise from primitive cells which have essentially the same capacity as the developing ovum and that the malignant trophoblastic elements of these tumors are derived from ectoderm in the same way as the comparable tissue in ordinary pregnancy. They consider that the cells from which these tumors arise are multipotential sex cells normally present in the adult testicle; these cells are probably spermatogonia. The authors think that the differentiated elements of the teratoma in testicular tumors are probably not responsible for any hormone production which may be observed, and that it is unlikely that any of the testicular tumors with the exception of the choriocarcinoma elaborate any hormone of themselves. They believe that the finding of gonadotrophic hormones in these other tumors suggests either undisclosed trophoblastic tissue or a systemic endocrine dysfunction which, as others have pointed out, may have preceded the occurrence of the tumor. —*E.C.R.,Jr.*

GREENE, R. D. B. E., A new synthetic estrogen. *Brit. M. J. 1:* 9–10 (1945).

The synthetic pro-estrogen alpha, alpha-di-(p-ethoxyphenyl)-beta-phenylbromethylene was administered to patients suffering with mild menopausal symptoms, to three cases with carcinoma of the prostate and three patients with uterine atrophy. In the six patients with vasomotor symptoms of the climacteric the drug given orally in doses of one to two grams brought relief from symptoms for two to three weeks. The good effects were maintained by weekly doses of 100 to 300 mg. The three cases of uterine atrophy showed little benefit but did not respond readily to other estrogens. It failed in carcinoma of the prostate; two patients who showed no improvement with D. B. E. responded dramatically to stilbestrol. The drug seems to be inferior to other synthetic estrogens in some respects and its only advantage is a prolonged action which allows weekly doses to be used.—*L.T.S.*

HUGGETT, A. ST. G. AND J. J. PRITCHARD. Experimental fetal death: the surviving placenta. *Proc. Roy. Soc. Med. 38:* 261 (1945).

The placental structure in rats was studied following fetal death produced by 1) crushing the embryos, 2) injection of pregnant mare's serum before the 12th day, 3) injection of estrone on the 9th day, 4) double ovariectomy *a*) on days seven to ten, *b*) on the 11th day and *c*) after the 12th day. Prior to days 11 and 12 estrone, pregnant mare's serum and bilateral ovariectomy caused decidual necrosis and death of the embryos, probably due to an alteration of the estrone/progesterone balance. Placentae survived after fetal death if the mesodermal-allantoic elements were differentiated.—*R.C.*

JONES, G. E. S. AND R. W. TELINDE. The curability of granulosa-cell tumors. *Am. J. Obst. & Gynec. 50* (6): 691–700 (1945).

The authors report three patients who developed recurrences of granulosa-cell tumor not less than 14 years after the original operation. All three have died, at 18, 20 and 21 years respectively, following the removal of the primary tumor in spite of the fact that the tumor originally gave no evidence of malignancy. All three were postmenopausal at the time of their recurrences and all showed clinical signs of estrogenic activity. Total urinary estrogen values were not extremely high in the two of them, falling within the range of values for normal cyclic women.—*C.D.D.*

KAPLAN, I. I. The effect of radiation on the function of the ovary in young girls: Supplementary report. *Am. J Obst. & Gynec. 50* (3): 340–341 (1945).

In 1939, the author reported a patient who at the age of 4½ years received intensive irradiation, x-ray and radium, for a pelvic tumor and who, in spite of this, subsequently had a normal menarche at 12. She continued to menstruate regularly until the age of 19. In 1943, this patient developed metastasis in the region of the coccyx and died a little more than one year later. The pathologic diagnosis was spindle-cell sarcoma, neurogenic type.—*C.D.D.*

MCINTOSH, C. B. AND W. E. BROWN. Adrenogenital pseudohermaphroditism treated with stilbestrol. *J. Pediat. 27:* 322 (1945).

The case is reported of a five-year-old child with the following features: 1) abnormally rapid growth rate with measurements equivalent to average for 7.5 years; 2) uncertain sex, although reared by parents as a girl; 3) physical examination essentially normal except for large size, tendency toward masculine physique, large amount of pubic hair of female pattern, a phallus 2.5 inches in length with a definite glans and prepuce but no urethral opening, a urethral orifice in the complete hypospadic position just below the phallus, well developed labia, small vaginal orifice partially obliterated by a membrane, and no testicles palpable; 4) excessive amounts of 17-ketosteroids in the urine; and 5) at exploratory laparotomy normal tubes and ovaries, a rudimentary uterus, and generalized enlargement of both adrenal glands. Part of one adrenal gland was removed and microscopic section revealed diffuse hyperplasia of the cortex. Roentgen therapy to the adrenal glands produced no change in the patient's appearance or in the size of the clitoris after an interval of two months. Oral stilbestrol (5 mg. daily for four months) caused development of the breasts, pigmentation of the nipples, and appearance of axillary hair, but no change in the size of the clitoris; however, with smaller doses of stilbestrol for 20 months there was a definite decrease in the size of the clitoris and a decrease in the rate of growth so that the child grew at a normal rate. At this time the epiphyses were found to be nearly closed, which might have been due to stilbestrol, so the estrogen was discontinued. Plastic operations consisting of amputation of the clitoris and extension of the vaginal orifice were successfully performed at the age of seven years. Attention is called to the fact that the patient had an older sibling with identical features who died of pneumonia at the age of six years, two years before the patient was first studied. Because of this history, the androgen excretion of the patient's mother was examined and was found to be normal in amount.—*E.C.R., Jr.*

RUBINSTEIN, B. B. AND H. S. GUTERMAN. A simple technique for preparing vaginal smears. *Am. J. Obst. & Gynec. 50* (5): 565–567 (1945).

The authors described in detail a simple and practical means of preparing vaginal smears which is adaptable to home and office use by the patient and for the physician. —*C.D.D.*

STEIN, I. F. Bilateral polycystic ovaries: significance in sterility. *Am. J. Obst. & Gynec. 50* (4): 385–398 (1945).

The author has studied 53 patients with bilateral polycystic ovaries. The diagnosis usually was based on a typical clinical syndrome, characterized by menstrual irregularity featuring amenorrhea, presumed sterility, masculine type of hirsutism, and less consistently, retarded breast development and obesity. The diagnosis was substantiated by demonstrating the ovarian lesions with pneumoperitoneum. The authors found endocrine therapy valueless. Bilateral wedge resection and suture of the ovaries was done in all instances. There were no recurrences and 64.5 per cent of the married women became pregnant.—*C.D.D.*

PATTON, G. C. Diethylstilbestrol in the treatment of functional ovarian disorders. *Am. J. Obst. & Gynec. 50* (4): 417–421 (1945).

The author treated 107 women with 232 functional ovarian complaints which included dysmenorrhea, simple cystic ovaries, irregularity in menstrual rhythm, profuse bleeding, and infertility. All patients received diethylstilbestrol, five milligrams orally daily for 20 days, therapy being started at the end of bleeding. The following results were recorded: partial or total relief in 56 per cent of dysmenorrheic patients; ovaries returned to normal size in 37 of 47 patients with cystic ovaries; in 13 of 14 patients with continuous uterine bleeding, hemostasis was produced in one to four days; 70 per cent of all menstrual disturbances were partially or entirely corrected; and in an admittedly incomplete study on infertile women, 26 per cent conceived.—*C.D.D.*

WATT, L. O. Endometrial biopsy curette. *Brit. M. J. 1:* 843 (1945).

An improved endometrial biopsy curette is described which is designed to give information in sterility investigations. The terminal cup is as short as possible allowing a biopsy to be taken from close to the fundus of the uterus and so give a much larger and longer strip of endometrium for histological section. The large, sharp, prominent edge of the curette cup improves the possibilities of getting an adequate sample of atrophic endometrium.—*L.T.S.*

WAY, S. D. B. E. in treatment of menopausal symptoms. *Brit. M. J. 1:* 10 (1946).

Eleven cases of menopausal disturbance were treated with D. B. E. Five were completely relieved of their symptoms, three were greatly improved and three failed to respond even after doses of three grams. The three patients who were improved but not completely relieved and two of the three failures were treated with stilbestrol and were almost completely relieved in three weeks after starting stilbestrol therapy. It appears from this small series that D. B. E. is probably not as effective as stilbestrol in the relief of menopausal symptoms and its sole advantage is that it needs to be administered infrequently.—*L.T.S.*

HYPOPHYSIS

COOKE, R. T. Simmonds' disease due to postpartum necrosis of the anterior pituitary gland. *Brit. M. J. 2:* 343 (1945).

A case of Simmonds' disease is described in a woman aged 59 due to necrosis of the anterior pituitary dating from a confinement twenty-seven years before. The patient showed a BMR of −37 per cent and a prolonged fall and greatly delayed return of the blood sugar on the administration of 1.4 units of insulin. The urinary 17-ketosteroids were zero. The patient died of cachexia and heart failure. On autopsy the pituitary appeared as a collapsed empty shell and adenocarcinoma of the pyloris was also present.—*L.T.S.*

DE ROBERTIS, E. AND E. DEL CONTE. A cytological method for the determination of the thyrotrophic hormone of the pituitary gland. *Rev. Soc. Argent. Biol. 20:* 88 (1944).

The authors have developed a quantitative method for the assay of the thyrotrophic hormone based on the amount of intracellular colloid in the thyroid gland. They have devised a cytological coefficient, which is defined as the ratio between the number of colloid droplets × 100 and the average diameter of the follicles. The sensitivity of the method was determined as follows: Young guinea pigs were injected with various doses of thyrotrophic hormone and 30 minutes later were sacrificed. The thyroid glands were frozen in liquid air, dried by the Altmann-Gersh method and stained with aniline blue-orange G stain. The glands showed a significant increase in the intracellular colloid even when treated with as little as 0.0002 Junkmann-Scoeller units of thyrotrophic hormone. The cytological coefficient increases with the dose, and as illustrated by a curve published in the paper, there exists an approximate proportion between this coefficient and the logarithm of the dose. A "guinea pig cytological unit" is devised; this is the amount of thyrotrophic hormone injected intravenously in a young guinea pig which will produce a fourfold increase in 30 minutes in the cytological coefficient of the control animal. The authors report that this cytological method can be applied to the assay of thyrotrophic hormone in organic fluids of normal and pathological individuals.—*F.A.de laB.*

MORGAN, J. Acromegaly with pregnancy. *Proc. Roy. Soc. Med. 38:* 326 (1945).

A case of a primipara, aged 34, who had been married seven years, and who had always suffered from headaches is reported briefly. The patient had not noted any change in the size of hands or feet or in facial appearance. She was first seen when three months pregnant and with well-developed acromegaly. An x-ray of the skull revealed enlargement of the pituitary fossa suggestive of a moderate-sized tumor. The symptoms had not progressed further by the 36th week of pregnancy.—*R.C.*

PISETSKY, J. E. Pituitary adenoma associated with chronic duodenal ulcer. *J. Nerv. & Ment. Dis. 102:* 537 (1945).

The author discusses the work of Cushing and others on the relationship of diencephalic-pituitary disorders and peptic ulcer. He then presents a case of pituitary adenoma with visual disturbances which date back 24 years. For more than eight years the patient

has had a chronic duodenal ulcer. Since irradiation of the tumor six years ago, with the exception of occasional gastric complaints, the symptoms have come to a relative standstill. The association of manifestations is accounted for on the basis that disturbances in impulse formation in the cerebral cortex and hypothalamus, as a result of pressure produced by the tumor, result in increased gastric peristalsis, hypersecretion and vasoconstriction which produce ischemia and then erosions, ulcerations or perforations of the stomach wall.—*R.G.H.*

PANCREAS

GREENBLATT, M., J. MURRAY, AND H. F. ROOT. Electroencephalographic studies in diabetes mellitus. *New England J. Med. 234:* 119–121 (1946).

A series of forty patients with uncomplicated diabetes and a series of thirty-five diabetic patients with repeated severe insulin reactions were studied for electroencephalographic abnormalities. The incidence of abnormal electroencephalograms in the series with uncomplicated diabetes was eight per cent which compares favorably with the range in unselected groups of non-diabetic persons. In the series of thirty-five patients with repeated insulin reactions eighteen showed definitely abnormal electroencephalograms. The authors conclude that the evidence supports the theory that severe repeated insulin reactions are due not only to unstable carbohydrate regulation but also to unstable cerebral function as well. They consider insulin sensitivity as evidence of an original underlying abnormality rather than a cause of the cortical changes, and that the electroencephalogram can be a definite aid in evaluating the stability of cortical function in diabetic patients.—*L.T.S.*

LIEBERMAN, A. A. Nervous and mental manifestations observed in spontaneous hypoglycaemia. (Elgin State Hospital.) *Elgin Papers. 5:* 43 (1944).

A case is presented of spontaneous hyperinsulinism due to pancreatic adenoma with chronic mental symptoms for three years and presented as recovered in the physical and mental aspects twenty months following surgery. Two cases of so-called functional hypoglycemia are presented as recovered upon dietary management alone, employing the high-protein, low-carbohydrate, moderate-fat diet. In such cases symptomatic relief may be obtained by administering carbohydrate in amounts too small to raise the blood-sugar titre. From the cases cited and evidence from the literature it appears that hypoglycemic states may manifest themselves as simulating any and all varieties of nervous and mental disorders. Emphasis is laid upon the remarkable reversibility of cerebral reactions in chronic hypoglycemia. The psychosomatic aspects of such cerebral reactions are emphasized.—*R.G.H.*

MALINS, J. M. Globin insulin: clinical trial. *Brit. M. J. 2:* 318–319 (1945).

Globin insulin was used in single daily doses in 36 cases of which 33 had had no previous treatment. All had a history of acute onset of diabetes. The diet was approximately the same for all patients. In ten cases perfect control, both clinical and biochemical, was obtained. The average dose in this group was twenty units. In sixteen cases control was

only fair. Hyperglycemia and glycosuria persisted although weight and general health were maintained. Insulin reactions frequently occurred in this group even when the dose was increased only to control the symptoms while hyperglycemia persisted. Six of this group have been changed to protamine zinc insulin with satisfactory results. In ten cases control was definitely inadequate and they were transferred to the protamine zinc insulin-regular insulin mixture. Globin insulin is considered to have a limited place in the treatment of mild and moderately severe diabetes.—*L.T.S.*

WECHSLER, H. F. AND J. I. WEIMER. Pancreatic lithiasis: a report of two cases in young adults. *Gastroenterology 5:* 181 (1945).

Two men, aged 27 and 28, respectively, had histories of digestive complaints and abdominal pain dating to the ages of ten and eight years, respectively. Bloating; nausea; vomiting; upper abdominal pain, not relieved by food and aggravated by fried and greasy foods; steatorrhea; a slight decrease in sugar tolerance; and the presence on roentgenography of multiple, irregular calcified shadows in the region of the pancreas completed the picture in each instance. One of the patients had been treated for renal colic; the other for peptic ulcer. The authors conclude that "the possibility of a pancreatic disturbance with eventual formation of demonstrable calculi must be considered in the differential diagnosis of recurrent attacks of upper abdominal pain of obscure etiology at any age period.—*T.H.McG.*

PARATHYROID

WIGLEY, J. E. M. AND D. HUNTER. Calcinosis in a case of chronic nephritis with secondary hyperparathyroidism. *Proc. Roy. Soc. Med. 38:* 141 (1945).

A case is reported with autopsy findings showing chronic nephritis and hyperplasia of all four of the parathyroid bodies.—*R.C.*

THE ASSOCIATION

FOR THE STUDY OF

INTERNAL SECRETIONS

PROGRAM OF THE TWENTY-EIGHTH ANNUAL MEETING

FRIDAY, AND SATURDAY, JUNE 28-29, 1946

Hotel St. Francis, San Francisco, California

GENERAL INFORMATION

Headquarters: St. Francis Hotel, San Francisco, California.

Registration: Everyone attending the meetings is requested to register. A fee of $1.00 will be charged non-members of the Association. Membership cards should be presented when registering.

The Scientific Sessions: The Scientific sessions will be held in the Colonial Room and programs will begin promptly on schedule. Papers presented at all meetings are planned for ten minutes and owing to the heavy schedule must be kept within this limit. Manuscripts of all papers should be submitted to the Secretary-Treasurer at the end of the presentation.

Annual Dinner: The Annual Dinner of the Association will be held on Friday evening, June 28, at 7:30 o'clock at the St. Francis Hotel in the Colonial Room preceded by cocktails at 6:30 in the Green Room.

Council Meetings: There will be a dinner meeting of the Council, together with all officers and members of the Publication Board, on Thursday, June 27, at the St. Francis Hotel at 6:00 o'clock. There will also be a Council breakfast on June 28; luncheon meeting on June 28; and luncheon meeting on June 29, for the same group. (See hotel bulletin board for location.)

Business Meeting: The Annual Business Meeting of the Association and Election of Officers will be held at 4:15 P.M., June 29, in the Colonial Room of the St. Francis Hotel.

Local Arrangements: Dr. Hans Lisser, Fitzhugh Building, Union Square, San Francisco 8, California, is in charge of the local arrangements for the meetings.

Secretary-Treasurer: Henry H. Turner, 1200 North Walker Street, Oklahoma City 2, Oklahoma.

IMPORTANT

Due to the general shortage of paper, copies of this program are necessarily limited. In the interest of economy and to avoid disappointment and inconvenience to yourself, PLEASE BRING THIS PROGRAM WITH YOU.

PROGRAM

FRIDAY, JUNE 28

8:30 A.M., Registration

I. 9:30 A.M. *Colonial Room*

CARL R. MOORE, presiding

1. PSYCHOSOMATIC ASPECTS OF ENDOCRINOLOGY
   FRIEDGOOD, HARRY B., *Department of Medicine, University of Southern California Medical School and the Los Angeles County Hospital, Los Angeles.*
2. PSYCHIC AND ENDOCRINE FACTORS IN OBESITY
   FREED, S. CHARLES, *San Francisco, California.*
3. CONTROL OF ENDOCRINE OBESITY
   KUNDE, M. M., *Northwestern University Medical School and Outpatient Endocrine Clinic of the Cook County Hospital, Chicago.*

DISCUSSION

4. THREE UNUSUAL NON-NEOPLASTIC OVARIAN ENDOCRINOPATHIES
   GOLDBERG, MINNIE B., ALICE F. MAXWELL (*by invitation*), *and* PEARL M. SMITH (*by invitation*), *Divisions of Medicine and Pathology, University of California Medical School, and the Hospital for Women and Children, San Francisco.*
5. BILATERAL CRYPTORCHIDISM IN IDENTICAL TWINS
   GLASS, S. J., *Los Angeles.*
6. CARCINOMA OF THE TESTIS
   REYNOLDS, RALPH ARTHUR, *San Francisco.*

DISCUSSION

7. PRELIMINARY REPORT ON PROTEIN-BOUND IODINE STUDIES IN THYROID DISEASES
   SOLEY, MAYO H., *University of California Hospital, San Francisco.*
8. ANATOMICAL EVIDENCE OF THYROID HYPOFUNCTION IN ALLOXAN INDUCED DIABETES MELLITUS
   BENNETT, LESLIE L. (*by invitation*), ALEXEI A. KONEFF (*by invitation*), *and* ADRIANNE P. APPLEGARTH (*by invitation*), *Institute of Experimental Biology, University of California, Berkeley.*
9. THE EFFECT OF ESTROGENS ON THE THYROID
   GASSNER, F. X., *Colorado Experiment Station, Fort Collins.*

DISCUSSION

10. FACTORS INFLUENCING INSULIN PRODUCTION
    ANDERSON, EVELYN, JOSEPH A. LONG (*by invitation*) *and* VIRGINIA SUTTON (*by invitation*), *Institute of Experimental Biology and Division of Medicine, University of California, Berkeley and San Francisco.*
11. BIOLOGICAL ASSAY OF INSULIN. OBJECTIVE DETERMINATION OF THE QUANTAL RESPONSE OF MICE.
    THOMPSON, R. E. (*introduced by* F. C. KOCH), *Pharmacology Section, Armour Laboratories, Chicago.*
12. INSULIN RESISTANCE: A CASE STUDY.
    MCGAVACK, THOS. H., SOLOMON D. KLOTZ (*by invitation*), MILDRED VOGEL (*by invitation*), *and* JAMES F. HART (*by invitation*), *New York Medical College, Metropolitan Hospital Research Unit, New York.*

DISCUSSION

II. 2:00 P.M. *Colonial Room*

13. THE EFFECTS OF GROWTH HORMONE AND ADRENOCORTICOTROPIC HORMONE ON THE URINARY GLUCOSE AND NITROGEN EXCRETION OF DIABETIC RATS.

BENNETT, LESLIE L. (*by invitation*), *and* CHOH HAO LI (*by invitation*), *Institute of Experimental Biology, University of California, Berkeley.*

14. A COMPARISON OF THE ACUTE EFFECTS OF CORTICOSTERONE AND 17-HYDROXY-CORTICOSTERONE ON BODY-WEIGHT AND THE URINARY EXCRETION OF SODIUM, CHLORIDE, POTASSIUM, NITROGEN AND GLUCOSE.
INGLE, DWIGHT J., RUTH SHEPPARD (*by invitation*), *and* MARVIN H. KUIZENGA (*by invitation*), *The Research Laboratories. The Upjohn Company, Kalamazoo.*

15. THE ISOLATION OF A NEW ACTIVE STEROID FROM THE ADRENAL CORTEX.
LOWENSTEIN, BERTRAND E. *and* R. L. ZWEMER. *Department of Anatomy, College of Physicians and Surgeons, Columbia University and Department of Pharmacotherapy, Harvard University Medical School.*

DISCUSSION

16. THE QUANTITATION OF AXILLARY HAIR GROWTH AS AN INDEX OF ENDOCRINE FUNCTION.
KINSELL, L. W., EDW. C. REIFENSTEIN, JR., DOROTHY BRYANT (*by invitation*), *and* FULLER ALBRIGHT, *Oakland and Boston.*

17. THE ASSESSMENT OF SOMATIC ANDROGYNY
BAYLEY, NANCY (*by invitation*), *and* LEONA M. BAYER, *Institute of Child Welfare of the University of California, and the Stanford University School of Medicine.*

18. SEXUAL BEHAVIOR OF THE BOVINE MALE USED IN ARTIFICIAL INSEMINATION.
HART, G. H., W. M. REGAN, *and* S. W. MEAD (*introduced by* H. H. COLE), *Division of Animal Husbandry, University of California, Davis.*

DISCUSSION

19. ENDOCRINE FEATURE AND TREATMENT OF CHRONIC CYSTIC MASTITIS AND THEIR RELATION TO INFERTILITY.
MORTON, JOSEPH H., *Dept. of Medicine, N. Y. Medical College, Flower & Fifth Avenue Hospitals—and the Endocrine Service of Dr. T. H. McGavack at Metropolitan Hospital.*

20. ARTIFICIAL REPRODUCTION OF THE CYCLIC CHANGES IN CERVICAL MUCUS IN HUMAN CASTRATES.
ABARBANEL, A. R., *Departments of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles.*

21. FURTHER STUDIES ON THE CONTROL OF MENORRHAGIA.
GREENBLATT, ROBERT B., *Department of Endocrinology, University of Georgia School of Medicine, Augusta.*

DISCUSSION

22. FACTORS CONCERNED IN THE MAINTENANCE OF FUNCTION OF THE CORPUS LUTEUM.
NELSON, W. O., *Department of Anatomy, College of Medicine, The State University of Iowa, Iowa City.*

23. INDUCTION OF OVULATION IN THE DIESTROUS MOUSE BY GONADOTROPINS.
SAUNDERS, FRANCIS J., *Research Laboratories of G. D. Searle & Company, Chicago.*

ANNUAL DINNER

III. 7:30 P.M. *Colonial Room, Hotel St. Francis.*

PRESENTATION OF THE E. R. SQUIBB & SONS AWARD FOR 1944–45.
PRESENTATION OF THE CIBA AWARD FOR 1944–45.
PHILIP E. SMITH, *Chairman of the Committee on Awards for 1944–45.*
PRESENTATION OF THE E. R. SQUIBB & SONS AWARD FOR 1945–46.
PRESENTATION OF THE CIBA AWARD FOR 1945–46.
WILLARD O. THOMPSON, *Chairman of the Committee on Awards for 1945–46.*

PRESIDENTIAL ADDRESS: CONTRIBUTIONS OF BABY OPOSSUMS TO ENDOCRINOLOGY

CARL R. MOORE, *The University of Chicago.*

SATURDAY, JUNE 29

IV. 9:00 A.M. *Colonial Room*

24. DIAGNOSIS OF HYDATIDIFORM MOLE BY GONADOTROPHIC HORMONE ASSAY USING THE SOUTH AFRICAN FROG.

    WEISMAN, ABNER I., *and* CHRISTOPHER W. COATES (*by invitation*), *Crow Creek Hospital, Ft. Thompson and New York.*

25. THE INFLUENCE OF VARIOUS HORMONES ON THE RESISTANCE OF SWISS MICE TO ADAPTED POLIOMYELITIS VIRUS.

    ANDERSON, JOHN A. *and* VERNON BOLIN (*by invitation*), *Department of Pediatrics, Salt Lake County Hospital, University of Utah, Salt Lake City.*

26. THE VALIDITY OF ENDOCRINE RESEARCH ON THE DOMESTIC NORWAY RAT.

    RICHTER, CURT P., *Phipps Clinic, The Johns Hopkins Hospital, Baltimore.*

DISCUSSION

27. DISCUSSION OF A SIMPLE, RAPID AND PRACTICAL MEANS OF DETERMINING URINARY GONADOTROPHINS IN PATIENTS.

    JUNGCK, EDWIN (*by invitation*), WILLIAM MADDOCK (*by invitation*), *and* CARL G. HELLER, *Departments of Physiology and Medicine, University of Oregon Medical School, Portland.*

28. GONADOTROPHINS IN NERVOUS EXHAUSTION DUE TO OVARIAN HYPOFUNCTION.

    HAWKINSON, L. F., *Oakland.*

29. EQUINE GONADOTROPIN. NINE YEARS OF CLINICAL EXPERIENCE.

    HALL, GEORGE J., *Sacramento.*

DISCUSSION

30. THE SYNERGISTIC ACTION OF PROGESTERONE WITH TESTOSTERONE PROPIONATE ON THE REPRODUCTIVE TRACT OF THE CASTRATE FEMALE OPOSSUM.

    MORGAN, CHARLES F., *Department of Pharmacology and Materia Medica, Georgetown University, Washington, D. C.*

31. THE SOURCE OF THE EXCESS CREATINE FOLLOWING ADMINISTRATION OF METHYLTESTOSTERONE.

    SAMUELS, LEO T., DOROTHY M. SELLERS (*by invitation*), *and* CARLEY J. MCCAULAY (*by invitation*), *Department of Biological Chemistry, School of Medicine, University of Utah, Salt Lake City.*

32. EXPERIMENTAL USE OF TESTOSTERONE IN PREMATURE INFANTS.

    SHELTON, E. KOST, *The Shelton Clinic, Los Angeles.*

DISCUSSION

33. CRANIOPHARYNGIOMA WITH INFANTILISM: CASE REPORT WITH CLINICAL AND PATHOLOGICAL STUDIES.

    MCGAVACK, THOS. H., RAYMOND HARRIS (*by invitation*), ANDREA SACCONE (*by invitation*) *and* HARRY GOLDBERG (*by invitation*), *New York Medical College, Metropolitan Research Unit, New York.*

34. CONTINUOUS GROWTH OF NORMAL RATS RECEIVING PURE GROWTH HORMONE.

    EVANS, H. M. (*by invitation*), MIRIAM E. SIMPSON (*by invitation*), *and* CHOH HAO LI (*by invitation*), *Institute of Experimental Biology, University of California, Berkeley.*

35. OBSERVATIONS ON THE USE OF THE SERUM PHOSPHORUS LEVEL AS AN

INDEX OF PITUITARY GROWTH HORMONE ACTIVITY; THE EFFECT OF ESTROGEN THERAPY IN ACROMEGALY.

REIFENSTEIN, EDWARD C., JR.; LAURENCE W. KINSELL; *and* FULLER ALBRIGHT, *Department of Medicine, Harvard Medical School and the Medical Service of Massachusetts General Hospital, Boston.*

36. FACTORS INFLUENCING THE PRODUCTION OF CARDIO-VASCULAR DISEASES BY ANTERIOR PITUITARY AND CORTICOID HORMONES.

SELYE, HANS, *Institute of Experimental Medicine and Surgery, University of Montreal, Canada.*

DISCUSSION

V. 2:00 P.M. *Colonial Room.*

37. THE SUBSTANCE IN LATE PREGNANCY MARE SERUM CAUSING OVARIAN INHIBITION.

COLE, H. H., *Division of Animal Husbandry, University of California, Davis.*

38. THE PROBLEMS OF ANTIGONADOTROPINS IN CLINICAL THERAPY.

LEATHEM, J. H., *and* A. E. RAKOFF, *Department of Zoology, Rutgers University, New Brunswick, and the Departments of Obstetrics and Gynecology and the Endocrine Laboratory, Jefferson Medical College and Hospital, Philadelphia.*

39. END RESULTS OF TREATMENT OF PITUITARY DWARFS WITH CHORIONIC GONADOTROPIN AND SEX HORMONES.

THOMPSON, W. O., N. J. HECKEL, *and* P. K. THOMPSON (*by invitation*), *Chicago.*

DISCUSSION

40. ADVANTAGES OF MODIFIED PROTAMINE ZINC INSULIN IN THE REGULATION OF DIABETES.

MACBRYDE, CYRIL M., *Los Angeles.*

41. EFFECT OF IODINE INTAKE ON THYROID IODINE DISTRIBUTION AND THYROID WEIGHT OF RATS TREATED WITH THIOURACIL AND OTHER GOITROGENS.

MACGINTY, D. A., *and* E. A. SHARP, *Research Laboratories, Parke, Davis & Company, Detroit.*

42. THE REVERSIBLE INACTIVATION OF THYROTROPIC HORMONE. ITS INACTIVATION BY THYROID TISSUE AND REACTIVATION BY THIOURACIL AND OTHER GOITROGENIC AGENTS.

RAWSON, RULON W., ALEXANDER ALBERT (*by invitation*), JANET W. MCARTHUR (*by invitation*), PRISCILLA MERRILL (*by invitation*), BEATRICE LENNON (*by invitation*), *and* CHARLOTTE RIDDELL (*by invitation*), *The Thyroid Clinic Massachusetts General Hospital, Boston.*

DISCUSSION

43. SENSITIVITY OF THE REPRODUCTIVE SYSTEM OF HYPOPHYSECTOMIZED FORTY-DAY-OLD MALE RATS TO TESTOSTERONE PROPIONATE.

SIMPSON, MIRIAM E. (*by invitation*) *and* HERBERT M. EVANS (*by invitation*), *Institute of Experimental Biology, University of California, Berkeley.*

44. THE SYNDROME OF CONGENITALLY ABSENT OVARIES, WITH INFANTILISM, HIGH URINARY GONADOTROPINS AND SHORT STATURE, WITH OTHER CONGENITAL ABNORMALITIES, SUCH AS SHORT WEBBED NECK, CUBITUS VALGUS, COARCTATION OF THE AORTA, ETC., AND TABULAR PRESENTATION OF TWENTY-ONE PREVIOUSLY UNPUBLISHED CASES.

LISSER, H., L. E. CURTIS (*by invitation*), ROBERTO F. ESCAMILLA, *and* MINNIE B. GOLDBERG, *Division of Medicine, University of California School of Medicine, San Francisco.*

45. ADRENAL ASCORBIC ACID RESPONSE TO ADRENOCORTICOTROPIC HORMONE IN INTACT AND HYPOPHYSECTOMIZED RATS.

MUNSON, PAUL L. *and* F. C. KOCH, *Biochemical Research Division, Armour and Company, Chicago.*

DISCUSSION

46. THE USE OF DESOXYCORTICOSTERONE ACETATE IN A BEESWAX MIXTURE FOR THE TREATMENT OF ADDISON'S DISEASE.
CODE, CHARLES F. (*by invitation*), EDWARD H. RYNEARSON, *and* MARSCHELLE H. POWER (*by invitation*), *Section on Clinical Physiology, Division of Medicine, and Section on Clinical Biochemistry, Mayo Foundation and Mayo Clinic, Rochester.*

47. LUTEOTROPHIC ACTION OF CHORIONIC GONADOTROPHIN IN THE WOMAN.
BROWN, W. E., *and* J. T. BRADBURY, *Department of Obstetrics and Gynecology, The State University of Iowa, Iowa City.*

DISCUSSION

VI. 4:15 P.M. *Colonial Room*

ANNUAL BUSINESS MEETING

VII. *Papers read by title.*

48. FURTHER OBSERVATIONS ON THE ABSORPTION OF SUBCUTANEOUSLY IMPLANTED PELLETS OF HORMONALLY ACTIVE STEROIDS.
MCGAVACK, THOMAS H. *and* HERMAN REINSTEIN (*by invitation*), *New York Medical College, Metropolitan Hospital Research Unit, New York.*

49. ABSENCE OF RENOTROPIC ACTION OF PURE ADRENOCORTICOTROPIC HORMONE (ACTH).
SIMPSON, MIRIAM E. (*by invitation*), CHOH HAO LI (*by invitation*), *and* HERBERT M. EVANS (*by invitation*), *Institute of Experimental Biology, University of California, Berkeley.*

50. THE RATE OF METABOLISM OF STEROID HORMONES BY THE LIVERS OF DIFFERENT SPECIES.
SAMUELS, LEO T., *and* C. J. MCCAULAY (*by invitation*), *Department of Biological Chemistry, School of Medicine, University of Utah, Salt Lake City.*

51. THE COMPARATIVE EFFECT OF VARIOUS GOITROGENIC AGENTS ON THE COLLECTION OF RADIOACTIVE IODINE BY THE THYROID IN RATS AND CHICKS.
RAWSON, RULON W., D. A. MCGINTY, *and* WENDELL PEACOCK (*by invitation*), *The Thyroid Clinic, Massachusetts General Hospital, Boston; the Research Laboratories, Parke Davis & Company, Detroit; and the Nuclear Physics Laboratories, Massachusetts Institute of Technology, Cambridge.*

52. TURNER'S SYNDROME. A CASE REPORT.
MOFFAT, WILLIAM M., *The Santa Barbara Clinic, Santa Barbara.*

53. INFLUENCE OF METABOLISM ENURESIS.
OSLUND, ROBERT M., *Ross-Loss Medical Group, Los Angeles.*

54. QUANTITATIVE INHIBITION OF OESTROGEN EFFECT ON CHICK OVIDUCT BY PROGESTERONE.
HERTZ, ROY, *National Institute of Health, Bethesda.*

55. THE EFFECT OF SUBCUTANEOUS ADMINISTRATION AND TOPICAL APPLICATION OF STEROID PREPARATIONS TO THE PIGMENTATION AREA OF THE HAMSTER.
KUPPERMAN, HERBERT S. *Department of Endocrinology, University of Georgia School of Medicine, Augusta.*

56. THE INFLUENCE OF THE ADRENAL CORTEX ON THE METABOLISM OF THE EVISCERATED RAT.
ROBERTS, SIDNEY (*by invitation*), *The Worcester Foundation for Experimental Biology, Shrewsbury.*

57. THE NATURE OF BENADRYL ACTIVITY: GLUCOSE TOLERANCE CURVES.
REINSTEIN, HERMAN (*by invitation*), *and* THOMAS H. MCGAVACK,

New York Medical College, Metropolitan Hospital Research Unit, New York.

58. NATURE AND DISTRIBUTION OF THE SKELETAL ABNORMALITIES IN CUSHING'S SYNDROME.
ALBRIGHT, FULLER, ANNE P. FORBES, *and* EDWARD C. REIFENSTEIN, JR., *Department of Medicine, Harvard Medical School and the Medical Service of Massachusetts General Hospital, Boston.*

59. MANAGEMENT OF THREATENED AND HABITUAL ABORTION BY LARGE DOSES OF ORAL ESTROGEN.
ABARBANEL, A. R., *Departments of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles.*

60. CLINICAL SYNDROMES OF ABERRATIONS IN CORPUS LUTEUM FUNCTION.
PARRETT, VIRGIL O. (*by invitation*), *and* A. R. ABARBANEL, *Departments of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles.*

61. PROBLEM OF 'CLOSED FALLOPIAN TUBES.' HORMONAL DIFFERENTIATION OF TUBES CLOSED BY SPASM FROM THOSE CLOSED BY ORGANIC PATHOLOGY BY MEANS OF METHYL TESTOSTERONE.
ABARBANEL, A. R., *Departments of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles.*

62. THE USE OF SODIUM PARA-AMINOBENZOATE PARENTERALLY IN THE TREATMENT OF HYPERTHYROIDISM.
BERMAN, LOUIS, *New York City.*

63. HYPOGONADOTROPHIC EUNUCHOIDISM—ITS CLINICAL AND LABORATORY DELINEATION FROM OTHER FORMS OF HYPOGONADISM WITH A DISCOURSE ON TREATMENT.
HELLER, CARL G. *and* WARREN O. NELSON, *Departments of Physiology and Medicine, University of Oregon Medical School, Portland, and Department of Anatomy, University of Iowa, Iowa City.*

64. DETERMINATION OF CORTICOSTEROIDS IN URINE.
LOWENSTEIN, B. E., A. C. CORCORAN, *and* IRVINE H. PAGE, *Research Division, Cleveland Clinic Foundation, Cleveland.*

65. THE EFFECT OF HYPOPHYSECTOMY ON THE TIME OF LAY OF THE HEN'S EGG.
ROTHCHILD, IRVING (*introduced by* RICHARD M. FRAPS), *Agricultural Research Center, U. S. Department of Agriculture, Beltsville, Maryland.*

66. PARATHYROPITUITARY SYNDROME IN PITUITARY BASOPHILISM.
PERLMAN, ROBERT M., *San Francisco.*

67. DIURNAL VARIATIONS IN THE LEVELS OF BLOOD GLUCOSE OF NORMAL HUMAN BEINGS SUBJECTED TO VARIOUS TYPES OF CALORIC RESTRICTION.
SCHWIMMER, DAVID (*by invitation*), *and* THOMAS H. MCGAVACK, *New York Medical College, Metropolitan Hospital Research Unit, New York.*

68. THE ROLE OF SEX HORMONES IN THE ORIGIN AND DEVELOPMENT OF ENDOMETRIAL GLANDS IN THE OPOSSUM.
MOORE, CARL R. *and* ELIZABETH A. FAILOR (*by invitation*), *Hull Zoological Laboratory, The University of Chicago, Chicago.*

ABSTRACTS

ARRANGED ACCORDING TO NUMBER

1. PSYCHOSOMATIC ASPECTS OF ENDOCRINOLOGY.
Harry B. Friedgood. From the Department of Medicine of the University of Southern California Medical School and the Los Angeles County Hospital, Los Angeles, California.

Carefully conducted observations were made of cases in which emotional conflicts precipitated endocrinopathies such as exophthalmic goiter, adiposogenital

dystrophy, amenorrhoea, meno-metrorrhagia, dysmenorrhoea and diabetes mellitus. Other cases were studied in which personality changes and abnormal emotional behavior resulted from hypothalamo-hypophysial tumors and from Cushing's syndrome due to adrenocortical neoplasm. These data indicate that the nervous system influences the functional activity of certain endocrine glands either by their innervation or through neuro-humoral means, and that an abnormal supply of hormones may affect the behavior pattern in certain circumstances.

Correlation of the available anatomical, physiological and clinical data discloses that the hypothalamo-hypophysial area plays an important role in the mechanism by means of which emotional conflicts directly or indirectly disturb the functional activity of certain endocrine organs.

2. Psychic and Endocrine Factors in Obesity.

S. Charles Freed. San Francisco.

Overweight is with rare exception a non-endocrine disturbance. It is a result of a positive caloric balance in which the patient expends less calories in energy than that which is taken in. The actual number of calories required for maintenance of weight may vary widely in different individuals thus accounting for popular misconceptions. The inability to control the intake of food at that level which maintains weight is due to underlying psychic drives. This tendency may be masked for many years or may be present from infancy. Many psychic factors will increase the urge to eat and the inability to control this urge. Other factors include disturbances in the endocrine system, organic diseases and others, but they all have one thing in common in that they increase the psychic or nervous tension of the individual. The most common endocrine disturbances in this regard are the menopause and premenstrual tension, and only occasionally a thyroid deficiency. The treatment of obesity is similar to that of many psychosomatic disturbances The first goal is that of inducing a sense of well-being in the patient by correcting any organic, endocrine or psychic disorder. In addition, benzedrine sulphate is a valuable drug for curbing the appetite and so establishing a high morale so that the patient is encouraged to continue depriving himself of the pleasure of eating. The use of thyroid is only rarely indicated, and often fails besides inducing harm from its toxic effects. Patients should receive psychiatric consultation where mild psychotherapy fails. Proper education of parents and emphasis on the psychological aspects of nutrition for children is advised.

3. Control of Endocrine Obesity.

M. M. Kunde. From the Northwestern University Medical School and the Outpatient Endocrine Clinic of the Cook County Hospital, Chicago.

The investigation of obesity presented in this study is characterixed by the fact that all cases herein reported were previously diagnosed as obese due to some endocrine dysfunction; in addition to the adiposity some patients gave evidence of specific gonad, thyroid or other endocrine dysfunction. In the treatment no endocrine product was used as part of the reducing therapy; reduction in weight was not based on calculated caloric intake but on re-education of the patient's dietary habits.

Physical examination and laboratory tests were made both at the beginning and at the end of the period of weight reduction. In some instances the laboratory findings were checked at the time when the patient had lost 50 pounds in body weight. Laboratory tests, in most cases, included basal metabolism, urinalysis, complete blood count, glucose tolerance, blood cholesterol, calcium and phosphorus, and x-ray of the pituitary. No patients with diabetes or marked hypothyroidism were included in this study. The advice and services of dietitians were not employed. Weight reduction in these patients was handled as any other major medical problem and patients reported directly to the physician at each visit. Charts, graphs and other significant data including weight loss up to one hundred pounds are presented.

4. Three Unusual Non-neoplastic Ovarian Endocrinopathies.

Minnie B. Goldberg, Alice F. Maxwell, and Pearl M. Smith, San Francisco. From the Divisions of Medicine and Pathology, University of California Medical School, and the Hospital for Women and Children, San Francisco.

The three cases with which this paper deals are being reported (1) because they are rare, and (2) because all were diagnosed preoperatively, verified by surgical exploration, and benefited by appropriate therapy.

I. Ovarian Agenesis

An eight-year-old girl was studied for five years because of failure to grow. Ovarian agenesis was suspected and verified by exploratory laparotomy at age thirteen. Early proof of diagnosis was sought in the hope of producing maximum growth before epiphyseal closure occurred. Stilbestrol therapy has been instituted. This is the youngest verified case on record.

II. Ovarian Hyperthecosis

An eighteen-year-old girl with primary amenorrhea, heterosexual hypertrichosis, virilism, acne and impaired carbohydrate tolerance had bilaterally enlarged ovaries. Hyperthecosis of the ovaries was suspected and proved pathologically. Bilateral partial ovarian resection resulted in prompt onset of normal and regularly recurring menses for the past year, and some improvement of the hypertrichosis, acne and carbohydrate tolerance.

III. Precocious Puberty

A six-year-old girl with evident secondary sex characteristics and an adult sized uterus bled per vaginam for eleven days. By exclusion an ovarian tumor was diagnosed despite lack of palpatory evidence. Surgical removal of a unilateral, enlarged, polycystic ovary was followed by regression of all signs of precocious puberty.

5. Bilateral Cryptorchidism in Identical Twins.

S. J. Glass. From the Endocrine Clinic—Cedars of Lebanon Hospital, Los Angeles, California.

The infrequency of reports of congenital sexual anomalies in twins prompts this report. A pair of identical twins presented themselves at age 9 with bilateral cryptorchidism. This was associated with mild stunting of growth and a poor nutritional status. There were no other significant anomalies. Treatment was directed to (1) attempts to induce spontaneous testicular descent with the aid of chorionic gonadotropin,—later supplemented with testosterone proprionate and methyl testosterone in minimal dosage, (2) improvement in nutrition. In two years of observation there was unilateral descent of the contralateral testis in each boy and descent to the external inguinal ring of the other testis. Considerable acceleration in skeletal and phallic growth accompanied the testicular descent. The nutritional status was likewise improved. Absence from the clinic has prevented further treatment.

6. Carcinoma of the Testis.

Ralph Arthur Reynolds. San Francisco, California.

Zondek, 1930, was the first to report that tumors of the testicle cause increased excretion of the gonadotropic hormone. This discovery has greatly accelerated interest in early diagnosis and treatment of tumors of the testis. The question of pathogenesis remains unchanged. There is still considerable confusion concerning the classification of testicular neoplasms. Correlation between their structure and the hormonal test is resulting in better classification. Chorion epithelioma causes five times the excretion of prolan A as noted in embryonic carcinoma. Persistence of prolan A excretion after excision of the tumor or after irradiation is presumptive evidence of metastasis and therefore of unfavorable prognosis.

A review of a study by Hinman of 85,000 male admissions to San Francisco

County and University of California Hospitals showed proved tumors of the testis in 52 or 1:1600. The relative frequency of testicular tumor among malignant tumors of all kinds is about 0.57%. Bilateral involvement, usually in cryptorchidism, is rare. The large majority of patients are between twenty and forty years. Julien, in 1925, collected 139 cases in infants. About 50% of testicular tumors belong to the differentiated type of the carcinomatous group of embryonal tumors. These afford the best prognosis. Primitive types of the carcinomatous group of embryonal tumors are highly malignant and offer a poor prognosis, although highly sensitive to irradiation. Radical surgical treatment of observed metastasis is of no use. Intensive irradiation alone is indicated.

Report of Two Cases

1. Twenty-seven year old male—Orchidectomy performed within three weeks after first observation by the patient. Patient living and well ten years later.
2. Thirty year old male—Reported swelling three and one-half months after first noted by patient. Extensive metastases already present, intensive irradiation instituted. Patient died eighteen months after orchidectomy. Both cases revealed tumors of adeno-carcinoma pattern.

7. Preliminary Report on Protein-Bound Iodine Studies in Thyroid Diseases.

Mayo H. Soley. University of California Hospital, San Francisco.

The determination of the protein-bound iodine in the serum of approximately 400 patients with various types of thyroid disease correlate well with the patients' clinical status and other indirect tests such as the basal metabolic rate, the plasma cholesterol and the oral galactose tolerance test. Sources of error such as previous administration of organic iodine (Priodax and other dyes for gall bladder visualization; Diodrast, Hippuran, Neo-Ipax, Skiodan, Lipiodol and other diagnostic agents) must be recognized.

Follow-up studies in patients with either Graves' disease or hypothyroidism indicate that the return of the clinical status to normal is associated with a similar reversion of the protein-bound iodine to normal levels.

8. Anatomical Evidence of Thyroid Hypofunction in Alloxan Induced Diabetes Mellitus.

Leslie L. Bennett, Alexei A. Koneff and Adrianne P. Applegarth. Institute of Experimental Biology, University of California.

Male rats were rendered diabetic by the intraperitoneal injection of alloxan. There was a reduction in both the relative and absolute thyroid weights in diabetic animals that was most marked in those with sustained severe diabetes. The mean thyroid weight of animals with diabetes of one month's duration was 16.0—0.8 mgm as compared with 40.3–2.6 mgm for the controls of the same age. Histologically the glands were characterized by small follicles, flattened epithelium, smaller and more darkly stained nuclei, and decreased vascularity. The Golgi apparatus was smaller and less elaborate and appeared as a small cap above the nucleus without the perinuclear extension seen in the normal control. The mitochondria were reduced in number and lost their tendency to be concentrated in the cytoplasm nearest the cell.

9. The Effect of Estrogens on the Thyroid.

F. X. Gassner. Colorado Experiment Station, Colorado State College, Fort Collins.

The thyroids, ovaries and uteri of 104 female rats were examined histologically to determine the effects of continued administration of natural and synthetic estrogens upon these organs, and to obtain information regarding thyroid-ovarian relationship. The animals were kept on a goitrogenic diet, low in iodine, and 3 out of the 6 groups received iodine in the form of KI. Four groups received either 30 gamma estrone or 9.4 gamma stilbestrol daily. The hyperplastic goiter produced in rats on the low-iodine diet was alleviated following administration of iodine. Estrogens given to rats on low-iodine diet reduced the goiter but caused

some degeneration of the thyroid parenchyma and lowered iodine storage. Of the two estrogens, diethylstilbestrol was more effective in this respect than was estrone. The storage of iodine in the thyroid glands of rats on low-iodine diet was not interfered with by estrogens when additional iodine was administered daily. This suggests that the effect of iodine on the thyroid is direct and not over the pituitary.

Epidermoid metaplasia occurred in the thyroids of all estrogen-treated rats. It is concluded that metaplasia was caused by the action of estrogens either upon the epithelium of pre-existing follicles because of their cellular duality, or upon embryonal remnants of the resorbed ultimobranchial body. It is not considered likely that an avitaminosis-A was present nor that a deficiency of this vitamin caused the metaplasia observed. The ovaries and uteri of the control rats were essentially normal. The ovaries of rats treated with estrogens showed severe atrophy, follicular atresia, interstitial fibrosis and occasional sub-mesovarial cyst formation. Corpora lutea were generally absent. The uteri of estrogen-treated rats showed squamous metaplasia of the endometrium with desquamation, vacuolar or hydropic degeneration and epithelial tufting. These changes varied in extent from small, focal lesions to total metaplasia of the entire lining of the uterine lumen. The few glands present were also altered.

The significance of certain pathological lesions found is discussed in the light of evidence presented by other workers. It is considered possible that some of the metaplastic areas may constitute a stage in the formation of precancerous foci.

10. Factors Influencing Insulin Production.

Evelyn Anderson, Joseph A. Long, and Virginia Sutton. Institute of Experimental Biology and Division of Medicine, University of California, Berkeley and San Francisco.

With the use of a small perfusion pump circulation was maintained in the isolated rat pancreas (including also the stomach, duodenum and mesentery) for two hours. Evidence of a living organ was demonstrated by its utilization of oxygen and glucose and by the stimulation of insulin production when the glucose in the blood perfusate was raised to 300 mg. per cent. The assay of insulin in the blood perfusate was done on demedullated, alloxan-treated, hypophysectomized rats.

Studies are being made to determine what conditions besides hyperglycemia will stimulate insulin production directly. A purified growth hormone preparation added to the perfusate did not stimulate the pancreas to produce insulin.

11. Biological Assay of Insulin. Objective Determination of the Quantal Response of Mice.

R. E. Thompson (Introduced by F. C. Koch). Pharmacology Section, Armour Laboratories, Chicago.

A simple method is described for the objective determination of the presence or absence of advanced insulin symptoms in mice. The method is utilized in the biological assay of insulin to eliminate personal bias and to reduce the cost of assay by making possible the further use of mice which would ordinarily be discarded. Personnel requirements are also reduced because the close observation of mice ordinarily required is eliminated.

The method consists of placing appropriate insulin treated groups of mice on separate 60° sloped wire mesh screens (24″×36″). A hundred or more mice may be placed on each such screen. The screens must be arranged so that the mice can come off only over a free edge 8 inches or more from any surface. The mice will remain on the screen until advanced insulin symptoms (convulsion, coma, muscular weakness) cause them to lose their foothold. They will then fall from the free edge of the screen into suitable trays after which they may be injected with glucose solution so they will recover for use in subsequent assays. Two hours after injection the mice remaining on the screens are counted. Difference from the original number gives the number of positive reactions. The customary treatment of these values gives the estimated potency of the sample insulin in terms of a standard.

Over 100 assays (200 mice each) have been completed by this procedure at room temperature. The procedure is shown to be equivalent in precision to the

usual procedure of detecting positive reactions by observation of mice in ordinary temperature controlled compartments.

This "sloped screen" procedure is adaptable to either room temperature or elevated temperature operation.

It is pointed out that this procedure for objectively determining a physiological "end-point" may be adaptable to other problems such as the bioassay of adrenocorticotropin and adrenocortical extract by anti-insulin activity and the quantitative study of hypnotics and anesthetics.

12. Insulin Resistance: A Case Study.

Thomas H. McGavack, Solomon D. Klotz, Mildred Vogel and James F. Hart. N. Y. Medical College, Metropolitan Hospital Research Unit.

A 64 year old man, whose diabetes began 7 years ago, demanded at that time as much as 920 units intramuscularly and 400 units intravenously daily to overcome glycosuria and ketonuria. Later he was able to do without insulin for 3 years. A second and a third period of "insulin insensitivity" have been observed, each associated with severe local reactions to insulin injections. As a result of studies during this third period, allergic antibodies to insulin were demonstrated repeatedly by the Kustner-Prausnitz method for passive transfer of sensitivity. Such reactions disappeared in from 10 to 12 weeks after the discontinuance of insulin and reappeared within from 10 days to 2 weeks upon resumption of the same. 'Benadryl' protected the patient from the development of insulin resistance due to these antibodies but did not cause their disappearance.

Effort was made to determine the presence of other substances in the blood and tissues of this patient which possessed a direct anti-insulinic action capable of protecting mice from ordinarily fatal doses of insulin. All attempts to demonstrate such a substance have failed, even when the patient was receiving 400 units of insulin daily and showing ketonuria and glycosuria of high degree.

It is concluded that insulin may act as an allergen; the development of antibodies may be so great that severe resistance to the action of insulin results. The data are discussed in relation to previous concepts of insulin resistance as revealed in the literature.

13. The Effects of Growth Hormone and Adrenocorticotropic Hormone on the Urinary Glucose and Nitrogen Excretion of Diabetic Rats.

Leslie L. Bennett and Choh Hao Li. Institute of Experimental Biology, University of California.

Rats with persistent diabetes mellitus induced by alloxan were maintanied on a constant food intake in metabolism cages. Urinary nitrogen and glucose were determined daily. The effects of three mgm per day of growth hormone and adrenocorticotropic hormone were studied. In each of thirteen experiments adrenocorticotropic hormone increased the degree of glycosuria and nitrogen excretion both with and without exogenous insulin administration. The increase in urinary glucose was greater than could be accounted for by gluconeogenesis from the extra protein catabolized under the influence of adrenocorticotropic hormone as measured by the rise in urinary nitrogen.

In seven of eight experiments without exogenous insulin, and in each of five experiments with exogenous insulin, growth hormone promoted protein storage as indicated by a decrease in urinary nitrogen excretion. In only five of the thirteen experiments with growth hormone was there a significant increase in glycosuria.

There is, therefore, in rats with alloxan induced diabetes a clear cut separation between the metabolic effects of growth hormone and adrenocorticotropic hormone. Only the adrenocorticotropic hormone produced a typical exacerbation of the diabetes with enhancement of both glycosuria and nitrogen excretion.

14. A Comparison of the Acute Effects of Corticosterone and 17-Hydroxy-Corticosterone on Body Weight and the Urinary Excretion of Sodium, Chloride, Potassium, Nitrogen and Glucose.

Dwight J. Ingle, Ruth Sheppard and Marvin H. Kuizenga. The Research Laboratories, The Upjohn Company, Kalamazoo.

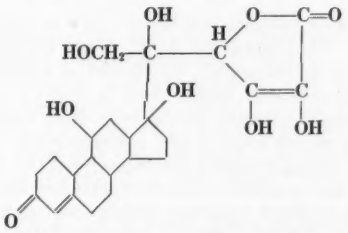
Normal male rats were force-fed a high carbohydrate diet. Five rats (total of 40) were tested at each dosage level of each of the two steroids. The administration of 5 mgm per day for five days of either corticosterone or 17-hydroxycorticosterone caused the excretion of glucose by some of the rats and a loss of weight and an increased excretion of sodium, chloride, potassium and nitrogen by all of them. The responses to the 17-oxygenated compound were greater than the responses to corticosterone. At dosage levels of 0.5, 1, and 2 mgm. per day for three days no glucose was excreted. At each dosage level 17-hydroxycorticosterone caused a loss of weight and an increased excretion of electrolytes and nitrogen to an extent which was proportional to the dose. At a dosage level of 2 mgm. per day corticosterone caused some inhibition of weight gain but did not have a consistent effect on the excretion of electrolytes and nitrogen. At dosage levels of 0.5 and 1 mg. per day, corticosterone caused some retention of sodium and of chloride but there was little effect on the excretion of potassium and nitrogen.

15. The Isolation of a New Active Steroid from the Adrenal Cortex.

Bertrand E. Lowenstein* and R. L. Zwemer.** From the Department of Anatomy, College of Physicians and Surgeons, Columbia University and the Department of Pharmacotherapy, Harvard University Medical School.

An attempt has been made to isolate an active compound from aqueous extracts of adrenal glands. Fresh adrenal glands were extracted with $CHCl_3$ in the presence of enough anhydrous Na_2SO_4 to remove all the water present. The extract was purified of inactive steroids by repeated distribution between water and benzene, and the active material finally adsorbed on a precipitate of colloidal $FeSO_4$ from an aqueous-alcoholic solution.

Purification of the active material thus adsorbed has resulted in the separation by fractional crystallization of dehydrocorticosterone, and of two hitherto unisolated compounds whose combined activity accounts for about 80% of the activity of the original aqueous extract. One of these compounds has been further characterized and is a ketonic steroid with empirical formula $C_{25}H_{34-36}O_9$. On mild hydrolysis in the absence of air ascorbic acid has been isolated and identified chemically and biologically. Oxidation with periodic acid or chromic acid yields adrenosterone. The following structural formula is tentatively ascribed to it:



Tests of the activity of this compound indicate that it is as active or more active than desoxycorticosterone in life-maintenance, somewhat less active in its effect on sodium retention, and about equal to dehydrocorticosterone as far as carbohydrate activity is concerned.

16. The Quantitation of Axillary Hair Growth as an Index of Endocrine Function.

Laurance W. Kinsell, Edw. C. Reifenstein Jr., Dorothy Bryant, and Fuller Albright. Massachusetts General Hospital, Boston.

* Present address: Research Division, Cleveland Clinic.

** Present address: Assoc. Chief, Division of Cultural Relations, State Department, Washington, D. C.

The growth of axillary hair has been quantitated in normal individuals, and in patients with various endocrinopathies. The work was undertaken on the hypothesis that there would be a direct correlation between the growth of genital hair and the excretion of 17 keto-steroids. This has been found to be true only in certain categories. There was however, found to be a direct correlation between the growth of axillary hair, and the local and systemic administration of androgen. Considerable data on axillary hair growth in idiopathic and endocrine hirsutism is presented, and correlated with keto-steroid out-put, and other objective laboratory data.

On the basis of the data so far obtained, it is felt that the quantitation of genital (axillary) hair represents a simple diagnostic measure of considerable usefulness in the evaluation of endocrinopathies.

17. The Assessment of Somatic Androgyny.

Nancy Bayley, and Leona M. Bayer. From the Institute of Child Welfare of the University of California, and the Stanford University School of Medicine.

A rating scale has been devised for assesing somatic androgyny in almost mature boys and girls. Standards are presented by body photographs; descriptions; a rating chart for constructing individual profiles. Subjects are rated according to degree and direction of sexual differentiation. Agreement between independent raters shows the scale to be reliable.

Scores fall into a bi-modal continuum with small amounts of overlapping of sexes. Cases with intermediate scores may be either undifferentiated (asexual), or show characteristics of the opposite sex (bisexual).

Androgyny appears to be truly a "mosaic," as Draper so aptly labeled it. Valid sex differences, having little or no overlap between masculine and feminine scores are almost entirely independent of each other within a sex. Many individuals may deviate in a few characteristics; few will deviate in many.

With standards for assessing somatic androgyny it should be possible to determine its relation to personality structure. Significant personality differences may well be found between those with normal builds; with relatively immature builds; with build characteristics of the opposite sex. Perhaps androgyny scores will also prove useful in relating sex variations in physique to other aspects of body build; to physical fitness; to hormone assays.

18. Sexual Behavior of the Bovine Male Used in Artificial Insemination.

G. H. Hart, W. M. Regan and S. W. Mead (Introduced by H. H. Cole). Division of Animal Husbandry, University of California, Davis.

Artificial insemination is now widely used in many countries of the world on several species of domestic animals, particularly dairy cattle and sheep. The techniques have been extensively studied and are reasonably well standardized.

One of the serious limiting factors is the behavior of the male in semen collection. Sexual libido, quality and quantity of the ejaculate and longevity of sperm activity are all factors subject to great variation within short periods of time in the same animal. Each animal manifests distinctly individualistic characteristics. Heredity and environment are both involved and need to be differentiated. Factors for sterility are evidently involved with good blood lines for production. Proven sires for transmitting ability with high fertility are to be desired in order to eliminate tendency toward male sterility. The paper sets forth the problem with some data without answering the questions involved.

19. Endocrine Feature and Treatment of Chronic Cystic Mastitis and Their Relation to Infertility.

Joseph H. Morton. From the Department of Medicine, N. Y. Medical College, Flower and Fifth Avenue Hospitals—and the Endocrine Service of Dr. T. H. McGavack at Metropolitan Hospital.

Mammary growth and development have been shown to be dependent largely upon the ovarian hormones. In general it has been accepted that estrogens mediate

the development of the mammary ducts and progesterone that of the lobular alveoli. The role played by the anterior pituitary is still not entirely clear.

The breast, like the endometrium, cyclically shows a proliferative phase induced by estrogens, and a secretory phase stimulated by progesterone. Excessive estrogenic activity, relative or absolute (with an associated diminution in progesterone), may result in abnormal changes known as chronic cystic mastitis.

The author stresses the frequent coincidence of chronic cystic mastitis and infertility in a group of women showing no gross pelvic pathology. In these patients special tests such as the basal metabolic rate, postcoital examination, tubal insufflation test and the seminal fluid were normal. The endometrial biopsies, however, showed evidence of hyperestrinism. The author concludes that the endometrial and mammary abnormalities are both manifestations of disturbed estrogen-progesterone balance.

Several methods of hormonal therapy, and also the place of irradiation and surgery in the management of chronic cystic mastitis are discussed and evaluated. Chorionic gonadotropin was found to be the most effective method of therapy.

20. Artificial Reproduction of the Cyclic Changes in Cervical Mucus in Human Castrates.

A. R. Abarbanel. Departments of Obstetrics and Gynecology, College of Medical Evangelists Los Angeles.

By means of estrogen (estradiol, diethylstillbestrol, hexestrol, estrone) the castrate's cervix was stimulated to secrete a clear glairy mucus which human sperm were able to penetrate and migrate through.

When progesterone or ethinyl testosterone (anhydro-oxy-progesterone) was given, the mucus became more viscid, decreased in volume, while sperm either were unable to penetrate or if they did, they soon bogged down. The relationship of these findings to the cervical factor in infertility is discussed.

21. Further Studies on the Control of Menorrhagia.

Robert B. Greenblatt. University of Georgia School of Medicine, Department of Endocrinology, Augusta, Georgia.

1. The examination of the endometrium soon after arrest of menorrhagia by estrogenic therapy usually reveals a hyperplastic or a proliferative endometrium.

2. When moderate doses of androgenic therapy are employed and bleeding is arrested, the endometrium is maintained apparently in the same status as prior to therapy.

3. When progesterone therapy is used and bleeding is arrested "according to plan," i.e. about 7–10 days after cessation of therapy, shedding of the endometrium occurs, comparable to that which occurs with normal physiologic menstruation. However, the loss of blood during the 7–10 day period may be excessive.

4. The administration of 25 mg. of testosterone propionate and 10 mg. of progesterone daily over a three day period results in almost immediate cessation of bleeding which, after an interval of 4 or 5 days, is followed by a short bout of withdrawal bleeding.

5. In the study, over a period of many years, of functional uterine bleeding, this method of therapy has thus far proved the most promising and ideal in the management of menorrhagia.

22. Factors Concerned in the Maintenance of Function of the Corpus Luteum.

Warren O. Nelson. University of Iowa, College of Medicine, Iowa City.

Estrogenic hormone appears to be a factor in the maintenance of functional activity in the corpora lutea of some species although the nature of this relationship may not be constant in the various forms. Administration of estrogen to adult female rats resulted in the maintenance of luteal function for 15 to 20 days, but did so only in the presence of the hypophysis. Removal of the hypophysis at any time during the course of treatment, i.e., during the course of pseudopregnancy, was followed by a return of the vaginal smear to an estrous state within a few days, as was true if the ovaries were removed.

Animals in which the hypophyses were removed during the course of pseudopregnancy, estrogen treatment being continued, returned to estrus when FSH, LH, chorionic gonadotrophin or pregnant mare serum were given. However, the administration of lactogenic hormone in such animals maintained the pseudopregnant state for as long as 20 days post-hypophysectomy. Suspension of treatment at any time in such animals was followed by the occurrence of vaginal estrus within three days. Animals sacrificed during the period of pseudopregnancy showed large corpora lutea, well-developed mammary glands, and mucified vaginae. Suitable stimulation of the uteri of pseudopregnant animals was followed by the development of deciduomata.

The effectiveness of preparations of lactogenic hormone in maintaining corpora lutea is attributed to the presence of the luteotrophic factor. The latter appears to be identical with the lactogenic hormone since the preparations show parallel activity of the two factors.

23. Induction of Ovulation in the Diestrous Mouse by Gonadotropins.

Francis J. Saunders. From the Research Laboratories of G. D. Searle & Co., Chicago.

Various gonadotropins were compared as to their ability to produce uterine weight increases in immature rats and ovulation in adult diestrous mice. After standardizing various preparations on the basis of their effectiveness in increasing uterine weight in immature rats, it was found that about 9 R.U. of pregnancy urine extract were required to cause ovulation in 50% of the mice, or about 4 or 5 R.U. of pregnant mare's serum. Extracts of pituitaries prepared by the same method, but from glands from different species, were studied as were also various types of extracts from sheep pituitary glands. It was found that 0.1 to 1.5 R.U. of the various pituitary extracts evoked ovulation in 50% of the mice.

24. Diagnosis of Hydatidiform Mole by Gonadotrophic Hormone Assay Using the South African Frog.

Abner I. Weisman and Christopher W. Coates (Ft. Thompson, S. Dak.) & (New York).

A simple and rapid method of assaying large amounts of chorionic gonadotrophic hormone excreted in the urine of patients with a suspected chorionic tumor (hydatidiform mole) is presented. By means of injecting varying dilutions of the suspected urine into pairs of the South African Frog (*Xenopus laevis*) a six-hour response is obtained. The reaction is an extrusion of ova following injection of the urine containing the hormone. The method used is to dilute the urine 1:10 and 1:100 and then inject one cubic centimeter of each dilution into each of two frogs. If the 1:100 dilution causes extrusion of ova in the frogs, the amount of gonadotrophic hormone can be assumed to be present in at least 100,000 frog units per liter. No other condition, but chorionic tumors of the hydatid variety, will evoke such a strong hormone response. This test may then be assumed as a specific test for hydatidiform mole. Six cases are reported to cite the pre-operative diagnosis by this method.

25. The Influence of Various Hormones on the Resistance of Swiss Mice to Adapted Poliomyelitis Virus.

John A. Anderson and Vernon Bolin. Dept. of Pediatrics, University of Utah, School of Medicine, Salt Lake City.

The nature of autarceologic immunity in man and animals to poliomyelitis virus is unknown. Spontaneous mouse poliomyelitis virus (Theilers) may infect 100% of Swiss mice yet only one in 2,000 animals succumb to paralysis. It is generally believed that a sub-clinical form of poliomyelitis affects the majority of a human urban community with development of only occasional paralytic conditions. Since estrogen treatment of animals reduces mortality from intranasal doses of an adapted poliomyelitis virus it has been suggested that physiological disturbances in metabolism of hormones may play a role in the autarceologic immunity of man.

Swiss mice capable of being orally infected with the adapted poliomyelitis virus (Jungeblut-Dalldorf MM strain) were treated with desoxycorticosterone acetate, progesterone, t-propionate and stilbesterol and the mortality rate to orally administered virus determined. Control and experimental animals were fed a dose required to kill 68% of the animals.

It was found that protection against the orally administered virus was provided in the following declining order—progesterone (complete protection), stilbesterol (mortality reduced from 68% to 2.5%), t-propionate (68% to 20%); desoxycorticosterone acetate failed to modify mortality.

It is possible that these substances modify mucous surfaces, preventing entry of the virus into the body, or stimulate effective immune responses.

26. The Validity of Endocrine Research on the Domestic Norway Rat.
Curt P. Richter. Phipps Clinic, Johns Hopkins Hospital, Baltimore.

Evidence gathered during the past few years indicates that the domestic Norway rat commonly used for all types of research in endocrinology and allied fields may be nothing more than an artificial creation of the laboratory experimenter produced by a long period of selective breeding under unnatural conditions.

This statement is based on comparisons made between domestic Norways and many thousand wild Norway rats recently trapped from the streets and alleys of a large city. These comparisons have revealed the existence of great differences in the anatomy, physiology, and responses to drugs in these two forms.

One of these differences which is of special interest to endocrinologists concerns the anatomy and function of the adrenal glands. In the domestic Norway the gland is about one-third as large as it is in the wild rat owing to a great atrophy of the cortex. (The medullas are about the same size.)

Adrenalectomy in the wild rat produces a much more pronounced state of shock. Even when they receive an amount of salt which suffices for domestic rats, these wild rats do not survive. They refuse to eat or drink, and die within two weeks. Clearly the adrenal cortex plays a much more important part in wild rats with their marked tension, fear, and anxiety, than it does in the tame, placid, domestic rats. Experiments are in progress to determine which of the various cortical extracts and in what amounts will be required to keep these rats alive. Clearly maintenance after adrenalectomy is a much more difficult problem than in the domestic rat.

A few of the other differences are that thiourea which has such a pronounced effect on the thyroid gland kills the domestic rat in doses as low as 3–5 mg. per kilogram body weight while 1–2 grams per kilogram body weight are required to kill a wild Norway rat.* Audiogenic stimulation which has no effect on the wild Norway throws the domestic Norway into violent and usually fatal fits and convulsions.

Thus it is possible that much of the research done on the domestic rat will have to be repeated and checked on the more normal wild Norway.

Simple methods for trapping, handling, and housing wild Norway rats will be described.

27. Discussion of a Simple, Rapid and Practical Means of Determining Urinary Gonadotrophins in Patients.
Edwin Jungck,* William Maddock, and Carl G. Heller. Departments of Physiology and Medicine, University of Oregon Medical School, Portland.

Simplicity, rapidity and efficiency are three prime criteria by which any method of assaying urinary gonadotrophins from patients must be judged, if such a method is to be widely adopted in clinical laboratories. Concentrating gonadotrophins from urine by filtering them through collodion membranes using pressure, dissolving the membranes, and then dissolving the active precipitates (as suggested

* Dieke, S. H. and C. P. Richter: Acute Toxicity of Thiourea to Rats in Relation to Age, Diet, Strain and Species Variation. Journal of Pharmacology and Experimental Therapeutics, *83:* 195, No. 3, March, 1945.

* Schering Research Fellow in Endocrinology.

by Gorbman) satisfies the requirements of simplicity and rapidity. To test the efficiency and practicability of this procedure, it was compared with recovery of gonadotrophins using the alcohol precipitation—dialysis—alcohol reprecipitation method.

Urinary gonadotrophin titers of normal males and females, and of patients having a wide variety of syndromes causing both high and low titers were compared. The results indicate that the recovery is less complete using the membrane technic; yet it is sufficiently great and simple to provide an excellent laboratory aid to clinical diagnosis of endocrine disorders.

Details of the method along with gonadotrophic hormone analyses of interesting cases will be presented.

28. Gonadotrophins in Nervous Exhaustion Due to Ovarian Hypofunction. L. F. Hawkinson. Oakland.

As in the menopausal syndrome, ovarian hypofunction previous to the climacteric often produces distressing symptoms. Equine gonadotrophin, used chiefly in the treatment of menstrual disturbances and sterility was employed in the present series of 460 cases. These patients complained of unpleasant symptoms which included nervousness, fatigability, headache and depression. The ovarian deficiency was usually temporary, nearly one-third followed pregnancy. Vaginal spreads were an aid in diagnosis, as well as in evaluation of treatment. When the syndrome was severe and in those with undesired sterility, one-two cyclic gonadotrophin therapy was used. Although the accompanying menstrual disorder was often corrected when symptoms were relieved, subjective symptoms tended to respond more readily. Subjective symptoms were relieved in 52.6%, and improvement was noted in 32.1%.

29. Equine Gonadotropin: Nine Years of Clinical Experience. George Joyce Hall. Sacramento.

Obviously different from the human gonadotropin factor of the anterior portion of the pituitary gland, equine gonadotropin seems at times to have stimulating clinical effects on hypofunctioning human ovaries.

Over twelve hundred patients have received P.M.S. (pregnant mare's serum) for the control of menstrual disturbances and sterility due to hypo-ovarian function during the past nine years.

We insist on the proper "preparation" of the patient before administration of the serum is justified. Control of the "symptoms" by substitution therapy, and obtaining a relatively normal phase of vaginal cornification on the 18th to 23rd day of the ovarian cycle is considered necessary before there is any reason to expect the P.M.S. to cause any improvement of ovarian function. Adequate clinical tests have been made of all patients before and throughout the therapy.

Statistical tables showing results of treatment will be presented, and an effort made to determine the percentage of those whose ovarian function seems normal, but who do not remain stabilized long enough without therapy to be properly classified as "cured."

Results obtained not only justify continued use of P.M.S. for the treatment of hypo-ovarian functional conditions, but seem to indicate more satisfactory results than are obtainable with any other gonadotropin therapy.

30. The Synergistic Action of Progesterone with Testosterone Propionate on the Reproductive Tract of the Castrate Female Opossum. Charles F. Morgan. Department of Pharmacology and Materia Medica, Georgetown University, School of Medicine, Washington, D. C.

Progesterone administered alone in 1 mg and 5 mg daily doses for twelve days to the castrate female resulted in a significant decrease in the weight (56%) and size of the reproductive tract as compared with the untreated castrate. The greatest decrease in size and weight was in the uterus.

Testosterone propionate administered alone for twelve days in 1 mg daily doses

did not significantly alter the weight or size of the tract but histological studies showed that the tissues were mildly stimulated. T-propionate given in 5 mg daily doses caused the weight and size to increase over the untreated castrate.

Progesterone, 1 mg/day, and t-propionate, 1 mg/day, given simultaneously for twelve days resulted in a synergistic action which increased the weights of the Müllerian duct derivatives of the reproductive tract to about 4 times those of the untreated castrate; about 8 times those of the castrate treated with the same dosage of progesterone alone; and about 4 times those which received the same dosage of t-propionate alone. The derivatives of the urogenital sinus were also affected by a combination of the two hormones, but to a lesser extent than were Müllerian duct derivatives. The synergism was also present when the daily dosage of t-propionate was increased to 5 mg in combination with 1 mg of progesterone.

Under the conditions of this experiment, (1) progesterone administered alone has no stimulating effect, but appears to cause regressive changes in the reproductive tract; (2) androgens administered alone show a stimulating effect; (3) a synergism between progesterone and t-propionate is manifested when the two hormones are administered simultaneously, and (4) progesterone apparently enhances the action of the androgen.

31. The Source of the Excess Creatine Following Administration of Methyltestosterone.

Leo T. Samuels, Dorothy M. Sellers, Carley J. McCaulay. Department of Biological Chemistry, University of Utah, Salt Lake City.

Since creatinemia and creatinuria do not follow administration of methyltestosterone in other animals, experiments were carried out on human beings with diseases of certain organs that might be involved in creatine metabolism. The following groups were studied: normal subjects, patients were severe liver damage, patients with nephrosis, and patients with severe nephritis. Blood and urine samples were collected before administration of methyltestosterone, after ten days of medication and at the end of twenty days' treatment with the drug. In the normal individual the plasma creatine was generally elevated at the end of the first ten days, but in adult males creatinuria did not always appear because of the low original creatinemia. Creatinemia appeared earlier in women and children, but, in all cases the creatine threshold lay between 0.7 and 1 mg/100 cc plasma. Creatinemia and creatinuria were produced in the cases suffering with hepatic damage, even when in a terminal condition. Creatinemia also appeared in the group suffering with nephrosis. The only cases where no large increase in plasma creatine occurred were those suffering with severe nephritis. Apparently the kidney is a primary factor in the excess creatine found after administration of methyltestosterone.

32. Experimental Use of Testosterone in Premature Infants.

E. Kost Shelton. Los Angeles.

Because of the nitrogen storage factor and other physiologic properties attributed to testosterone, preparations of this substance were administered to premature infants in the hope of stimulating the vital processes measured by survival. The results were encouraging.

33. Craniopharyngioma with Infantilism: Case Report with Clinical and Pathological Studies.

Thomas H. McGavack, Raymond Harris, Andrea Saccone and Harry Goldberg. New York Medical College, Metropolitan Research Unit.

Death of a man at age 54, with first symptoms at age of 15, was preceded by five years continuous observation during which prolonged treatments included methyl testosterone, t-propionate, desoxycorticosterone acetate, alpha-estradiol dipropionate, desiccated thyroid and pituitary preparations; diets of known sodium, carbohydrate, protein and fat were used.

Post-mortem revealed a lack of normal anterior pituitary and the presence of a

calcified craniophraryngioma 4×4×3 cm. Organ weights in grams w[illegible]e thyroid and parathyroids 9.7; right testicle, 2.8; left testicle plus testostero[illegible]nplant, 4.4; adrenals—right 3.6, left 3.3; prostate, 10.2; pancreas, 49.1; thym[illegible] weighable.

Subjective improvements always followed testosterone therapy (25 mgs or more 3 times weekly) or desiccated thyroid (15-200 mgs daily) or a combination of these. Flat intra-venous glucose tolerance curves of untreated periods became normal under testosterone therapy but were not altered by other treatments; high cholesterol was reduced to normal by thyroid but unmodified by other medicants. Blood potassium was low, sodium high, with treatments of estradiol and desoxycorticosterone acetate. Fluid intake and urine output rose from 1.0 liter to 3.5 liters per day with desoxycorticosterone, 15 mgs daily, and a diet containing 2.6 gms sodium. Urinary creatine was decreased by t-propionate, increased by methyl testosterone, unchanged by other agents. Low insulin clearances were elevated by DCA and less by t-propionate. Capillary permeability was increased from minus 22% to plus 33% by DCA and less by estradiol; lowest values occurred with thyroid. Kepler-Robinson water tests similar to those in Addison's disease were not altered by treatment. Pituitary extract were ineffective in this patient

34. Continuous Growth of Normal Rats Receiving Pure Growth Hormone.
Herbert M. Evans, Miriam E. Simpson, and Choh Hao Li. Institute of Experimental Biology, University of California.

Normal, adult, plateaued, female rats (211 days old) have been injected 6 days weekly for 436 days with anterior hypophyseal growth hormone. The initial dose of 0.4 mg was gradually increased to 2 mg. Growth continued during the whole period, the experiment being terminated due to the advanced age of the animals. The greatest weight attained was 662 gm. The range of final weights in the experimental and control groups did not overlap; the smallest experimental rat weighed 410 g. the largest control 353 g. The average gain of 8 experimental rats was 293 g, of 5 controls 57 g. The average body length at autopsy of the experimental rats was 45.5 cm, of the controls 40.9 cm. Liver, kidneys, heart, stomach and intestine increased in weight in proportion to body weight. The thymus was not hypertrophied as occurs upon acute administration of growth hormone. The other endocrine organs were not increased in proportion to body weight, as might be anticipated from the absence of the specific hormonal stimulants in the growth hormone injected.

36. Observations on the Use of the Serum Phosphorus Level as an Index of Pituitary Growth Hormone Activity; The Effect of Estrogen Therapy in Acromegaly.
Edward C. Reifenstein, Jr., Laurence W. Kinsell,; and Fuller Albright. From the Department of Medicine of the Harvard Medical School and from the Medical Service of the Massachusetts General Hospital, Boston.

Three observations are presented in this paper: (1) The serum "inorganic" phosphorus level is elevated without a corresponding fall in the serum calcium level in most acromegalic patients; the same is true in growing children. (2) The high serum phosphorus level and many of the symptoms of acromegaly respond to estrogen therapy. Since it is known from the literature that the administration of estrogen alone inhibits growth in animals and that the simultaneous administration of growth hormone with estrogen prevents this inhibition, it is suggested that (other factors being equal) a high serum phosphorus level may be an index of pituitary growth hormone activity. (3) The negative calcium balance (a common finding in acromegaly) responds to estrogen therapy as does the calcium balance of post-menopausal osteoporosis. The evidence for the above observations and a discussion of certain implications, both academic and clinical, is given in this presentation.

36. Factors Influencing the Production of Cardio-Vascular Diseases by Anterior Pituitary and Corticoid Hormones.

Hans Selye. From The Institute of Experimental Medicine and Surgery, University of Montreal, Montreal, Canada.

Both desoxycorticosterone acetate (DCA) and lyophilized anterior pituitary tissue (LAP) produce malignant hypertension, nephrosclerosis, periarteritis nodosa of the cardiac vessels and myocarditis (with nodules resembling Aschoff's bodies) in the rat.

Unilateral nephrectomy and a high NaCl or a high protein intake sensitize the rat to these toxic effects of both DCA and LAP; "acidifying salts" (e.g. NH_4Cl or $CaCl_2$) and low protein diets have an opposite effect.

Low protein diets also inhibit, and high protein diets enhance the ability of LAP to cause adrenal cortical hypertrophy.

In the adrenalectomized animal, none of the above-mentioned LAP overdosage manifestations are evident; hence, LAP probably acts because of its adrenotropic hormone content which causes the adrenal cortex to elaborate DCA-like corticoids.

In the case of DCA overdosage, the above-mentioned changes are accompanied by hypopotassemia, hypochloremia and periarteritis nodosa of the mesenteric vessels, while LAP treatment rarely produces these latter changes.

The cause of the slight qualitative differences between the actions of DCA and LAP have not as yet been elucidated. It is possible that the anterior pituitary produces substances which inhibit some of the actions of DCA, or that the natural (endogenous) corticoids liberated by the adrenal, under the influence of LAP, are qualitatively slightly different from DCA.

In rats sensitized by NaCl and unilateral nephrectomy, various types of nonspecific damage (e.g. cold) produce lesions similar to those elicited by LAP or DCA. The theory is advanced that the spontaneous diseases of human pathology, which are imitated by LAP or DCA overdosage, are due to a defensive increase in the production of corticotropic and corticoid hormones. The above-mentioned cardio-vascular lesions could then be regarded as by-products of this adaptive defence reaction; that is, as "Diseases of Adaption." (Subsidized by a grant of the Commonwealth Fund).

37. The Substance in Late Pregnancy Mare Serum Causing Ovarian Inhibition.

H. H. Cole. Division of Animal Husbandry, University of California, Davis.

In earlier studies, we (Cole and Hart, 1930) showed that, whereas the serum of mares in early stages of pregnancy contained large amounts of a gonadotrophin, in late pregnancy the serum inhibited ovarian activity in the immature rat. Furthermore, the ovaries of the mare in late pregnancy regress to a remarkable degree and are devoid of both corpora lutea and large follicles.

Because of the large amounts of gonadotrophin present in early pregnancy, the possibility existed that an antigonadotrophin was formed. Tests for antigonadotrophin were negative, however—a further substantiation of the concept enunciated by Leathem and Rakoff that gonadotrophins of homologous source are not antigenic.

Tests for lactogenic hormone, another substance producing ovarian inhibition, were likewise negative.

The evidence at hand indicates that the inhibition is due to estrogens present in the blood in low concentration. The inhibition produced by late pregnancy serum has been compared to that obtained with estradiol benzoate (Progynon B). In both instances, inhibition occurs if a dose is given equivalent to about one-fourth R.U. daily. Estrogens in the urine of pregnant mares produce a similar inhibition at comparable dosage levels.

The role which estrogens play in regulating gonadotrophic secretion will be discussed.

38. The Problem of Antigonadotropins in Clinical Therapy.

J. H. Leathem and A. E. Rakoff. From the Department of Zoology, Rutgers University, New Brunswick, and the Departments of Obstetrics and Gynecology and the Endocrine Laboratory, Jefferson Medical College and Hospital, Philadelphia.

Adequate clinical evidence is available to show that antagonists against equine gonadotropin and synapoidin (sheep pituitary and chorionic gonadotropin) develop in the serum during therapy. Antihormones persist for at least three months and with synapoidin the titres could be correlated with the response to therapy in cases of functional bleeding.

To establish a rationale for prolonged therapy, hormone specificity of antihormones was studied. Serum from patients treated for two to five months with synapoidin failed to reveal antagonists to synapoidin, equine gonadotropin, equine pituitary, chorionic gonadotropin or human pituitary with but one exception in which chorionic gonadotropin was inhibited. Patients who developed antihormones against synapoidin revealed that the antiserum would not antagonize the action of human pituitary but did inhibit equine gonadotropin and chorionic gonadotropin. The non-specific nature of the antiserum is indicated.

Two patients developed antihormones to equine gonadotropin but the serum did not antagonize the action of human pituitary or synapoidin. The antiserum formed against equine gonadotropin appears to be hormone specific.

Synapoidin and equine gonadotropin were administered to one patient at different times and the serum when tested was capable of inhibiting equine gonadotropin and chorionic gonadotropin but did not influence synapoidin.

39. End Results of Treatment of Pituitary Dwarfs with Chorionic Gonadotropin and Sex Hormones.

W. O. Thompson, N. J. Heckel, and P. K. Thompson, Chicago.

Observations on the treatment of pituitary dwarfs during the last sixteen years warrant the following conclusions:

The only way in which growth can be accelerated in male pituitary dwarfs is by the administration of chorionic gonadotropin or male sex hormone. These materials insure that the growth component associated with puberty takes place and are therefore of value only if the gonadotropic-producing mechanism of the pituitary is deficient. They are in no sense a substitute for the thyroid hormone or for the growth factor of the pituitary. They influence growth by inducing puberty and causing the acceleration of growth and skeletal molding associated with puberty. The maximum acceleration of growth associated with the administration of these materials in the male pituitary dwarf is about 10 inches and the optimum time for starting the administration appears to be the eleventh or twelfth year.

In the female pituitary dwarf the administration of female sex hormone causes some acceleration of growth, although not as much as the male sex hormone in the male pituitary dwarf.

The thyroid hormone and various commercial preparations of the growth factor of the pituitary are not effective in stimulating growth in pituitary dwarfs.

Pituitary dwarfs treated with chorionic gonadotropin and the sex hormones remain short because they show only that increment of growth associated with puberty and there is no way at present of making up for the deficiency of pituitary growth factor.

40. Advantages of Modified Protamine Zinc Insulin in the Regulation of Diabetes.

Cyril M. MacBryde. Los Angeles.

A modification of protamine zinc insulin containing 0.5 mg. of protamine per 100 units (instead of the standard 1.2 mg.) has 25 per cent of the insulin content

in soluble, quickly-absorbed form, while 75 per cent is in the precipitate and is slowly absorbed over a period exceeding 24 hours. Maintenance therapy with this MPZ insulin has proved very satisfactory, direct comparative studies having shown better control with it than with insulin mixtures, globin insulin and other modified insulins.

The majority of patients needing 40 units or less of insulin daily can be well regulated with a single daily dose of standard PZ insulin. Of a series of 385 diabetic patients studied during a six year period, 233 (58 per cent) were well controlled with standard PZ insulin. The remaining 152 needed over 40 units daily and could not be regulated with standard PZ insulin, but 90 per cent of this group of severe diabetic patients were well controlled with MPZ insulin. Strength, energy and nutrition are better than with any other treatment program, and the incidence of complications has been reduced. Individual case studies of patients needing as much as 100 units daily illustrate the superiority of MPZ insulin, a more nearly normal 24 hour blood glucose curve being established with an undistorted diet and only one daily injection being required.

41. Effect of Iodine Intake on Thyroid Iodine Distribution and Thyroid Weight of Rats Treated with Thiouracil and Other Goitrogens.

D. A. McGinty and E. A. Sharp. Research Laboratories, Parke, Davis & Company, Detroit.

Absorption of iodine (Rawson and collaborators, 1944) and formation of diiodotyrosine and thyroxin (Franklin and associates, 1944) by the thyroid of the rat is inhibited during thiouracil treatment provided iodine intake is at or near physiological requirements. If, under the same conditions, iodide is added to the drinking water in increasing concentrations, iodine accumulates in the thyroid gland in amounts proportional to increased intakes. Fractionation of thyroids from such animals by means of $Zn(SO_4)_2$ and NaOH indicates, however, that practically all of the iodine exists in non-protein-bound form presumably as inorganic iodide. Since the iodine concentration in other organs under the same experimental conditions was much smaller, Salters suggestion (1945) that a loose combination of iodide and thyroid protein exists, is given support. Equivalent amounts of iodine as iodate or as diiodotyrosine also occur in $Zn(OH)_2$ supernatants if given with thiouracil in the diet. In control experiments without thiouracil, added iodine caused an increase only in the protein-bound fraction of thyroid. The goitrogenic effect of thiouracil as well as that of certain other antithyroid substances studied, persists during high iodine intakes although some decrease in degree of thyroid hypertrophy was noted.

42. The Reversible Inactivation of Thyrotropic Hormone. Its Inactivation by Thyroid Tissue and Reactivation by Thiouracil and Other Goitrogenic Agents.

Rulon W. Rawson, Alexander Albert, Janet W. McArthur, Priscilla Merrill, Beatrice Lennon, and Charlotte Riddell. From the Thyroid Clinic of the Massachusetts General Hospital, Boston.

Explanted slices of normal rabbit thyroids were bathed in Tyrode's solution containing thyrotropic hormone at a temperature of 37°C. After a forty-eight hour period of incubation, the medium was removed and assayed. It was observed that exposure of 10 Junkmann Schoeller units of thyrotropic hormone to slices of one rabbit thyroid resulted in a complete loss of thyroid stimulating effect.

The inactivated hormone was treated with thiouracil and other goitrogenic drugs and assayed. After mixing or after incubation with these agents, the inactivated hormone was observed to recover in varying degrees its thyroid stimulating action. These agents in the amounts used to reactivate the inactive hormone when administered alone had no measurable effect on thyroids of the test animals.

Active hormone after incubation with these goitrogens was found to have a greater thyroid stimulating action than untreated active hormone. The same

augmentation was observed after the goiter producing agents had been removed by dialysis.

The theory is advanced that the action of certain goitrogens is at least twofold: that they interfere with thyroid hormone production and that in addition they augment the action of thyrotropic hormone.

43. Sensitivity of the Reproductive System of Hypophysectomized Forty-day-old Male Rats to Testosterone Propionate.

Miriam E. Simpson and Herbert M. Evans. Institute of Experimental Biology, University of California.

In a previous paper (Simpson, M. E., C. H. Li and H. M. Evans: Endocrinology *35:* 96, 1944) it was reported that the testicular tubules of 40-day-old male rats were maintained and even caused to continue development during the 15 days following hypophysectomy when injected with extremely small doses of ICSH. Tubular stimulation, in fact, occurred at doses too low to prevent the accessory organs of reproduction from regressing to the hypophysectomized condition. As it has been assumed that ICSH acts indirectly through the male sex hormone produced, similarly prepared test animals were injected with varying doses of testosterone propionate to compare androgenic with gametogenic effects. This substance (in contrast with ICSH) proved equally good as a stimulant of testicular tubules and accessories. These findings do not sustain the explanation cited for the mode of action of ICSH on the testicular tubules.

44. The Syndrome of Congenitally Absent Ovaries, with Infantilism, High Urinary Gonadotropins and Short Stature, with Other Congenital Abnormalities, such as Short Webbed Neck, Cubitus Valgus, Coarctation of the Aorta, etc., and Tabular Presentation of Twenty-One Previously Unpublished Cases.

H. Lisser, L. E. Curtis, Roberto F. Escamilla, and Minnie B. Goldberg. From the Division of Medicine, University of California Medical School, San Francisco, California.

About 50 cases of this syndrome have been published. We are adding 21 cases. The absence of ovaries has been demonstrated in 20 previously reported cases and in 4 of our patients, one of whom was only 13 years old. Urinary gonadotropins tested in 10 of our cases were abnormally high. Two of the remaining 11, however, were verified pathologically. The remaining 9 patients are characteristic clinically. Photographs are available for all but 2 of our 21 cases.

The absence of ovaries is considered responsible for the amenorrhea, absent mammary development, sparse sexual hair and high urinary gonadotropins—but not for the shortness. The latter may be the result of a germinal defect, like the ovarian agenesis and other congenital abnormalities. The shortness would be difficult to explain on a hormonal basis. For contrast, a photograph of a tall female, age 33, who was castrated at the age of 5, will be shown.

Early diagnosis is stressed so that measures to promote growth can be instituted, especially because the "bone-age" is usually only slightly retarded.

Estrogens are highly beneficial in causing breast development, growth of sexual hair, and, if given in cyclic fashion, regular withdrawal bleeding, with consequent profound improvement in morale.

45. Adrenal Ascorbic Acid Response to Adrenocorticotropic Hormone in Intact and Hypophysectomixed Rats.

Paul L. Munson and F. C. Koch. Biochemical Research Division, Armour and Company, Chicago.

Single subcutaneous injections of purified adrenocorticotropic hormone (ACTH) into normal male rats decreased adrenal ascorbic acid concentrations one hour later as follows:

ACTH administered	No. of rats	Adrenal ascorbic acid: decrease from controls
gammas		per cent
2.5–5	36	3
10	29	8
20–25	40	18
40–50	34	20
80	30	22
100	11	42
160–400	32	39

Thirteen successive daily injections of purified ACTH into hypophysectomized male rats raised the ascorbic acid content of the adrenals as follows:

Daily dosage ACTH	No. of rats	Adrenal ascorbic acid
		gammas per rat
Saline only	63	27.4
40 gammas	67	38.2
200 gammas	68	43.7
0.8–1 mg.	28	52.1
Unoperated	13	85.0

When ACTH was administered at a level sufficiently high to increase the adrenal weight above that of unoperated controls the adrenal ascorbic acid of the treated group was still significantly less than that of the controls. Prolongation of the interval between last injection and autopsy from 24 to 48 hours did not change the values significantly.

Although we have demonstrated the existence of a quantitative relationship between ACTH dosage and adrenal ascorbic acid response both in intact and hypophysectomized rats, animal variation is high and the slope of the curve relating log-dosage and response is low. It is concluded that neither procedure will lead to an improvement over bioassay methods previously described. On the other hand, the recently introduced method of Sayers and Sayers (Fed. Proc. *5*, 200 (1946)), using a single intravenous injection of ACTH in one-day hypophysectomized rats, has worked well in our hands, and we believe it shows promise.

46. The Use of Desoxycorticosterone Acetate in a Beeswax Mixture for the Treatment of Addison's Disease.

Charles F. Code, Edward H. Rynearson, and Marschelle H. Power. Section on Clinical Physiology, Division of Medicine, and Section on Clinical Biochemistry, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Beeswax mixtures have been used for the administration of histamine, heparin, penicillin and other substances in cases in which a delay in absorption is advantageous. In the treatment of Addison's disease, desoxycorticosterone acetate has been administered both in oil and as pellets. We have studied its injection in a beeswax mixture in fourteen cases. Three of the patients have died and their deaths will be discussed. Of the remaining eleven patients, two have had only one or two injections, six have had five to eight injections and three have had ten to twenty injections. The three patients who have had more than ten injections have now been treated for several years by this method. Their experience will be reported in detail.

47. Luteotrophic Action of Chorionic Gonadotrophin in the Woman.

W. E. Brown and J. T. Bradbury. Department of Obstetrics and Gynecology, State University of Iowa.

Two women were given chorionic gonadotrophin (Antuitrin-S) in doses of 20,000

I.U. per day. Treatment was started in the late luteal phase of the menstrual cycle and was continued until the onset of bleeding. Endometrial biopsies were obtained once a week, before, during and after treatment as a means of determining the sequence of changes in ovarian activity. The endometrium of these two women had gone through the normal sequence of changes since the last menstrual period and was a typically premenstrual secretory endometrium at the time of the initial injection. Menstruation was delayed 2 weeks beyond its expected date of onset in one patient, and was delayed 3 weeks in the second patient. The endometrial biopsies obtained during this interval of treatment were definitely secretory and had a marked decidual reaction (deciduoid??). The continued maintenance of this luteal endometrium indicates that the chorionic gonadotrophin has a definite luteotrophic action in the woman. The negative results in our realier report Brown, Bradbury and Metzger (1941) were undoubtedly due to the low doses employed. These studies are being expanded and will be reported in detail.

48. Further Observations on the Absorption of Subcutaneously Implanted Pellets of Hormonally Active Steroids.

Thomas H. McGavack and Herman Reinstein. N. Y. Medical College, Metropolitan Hospital Research Unit.

The rate of absorption of 75 mg. pellets of desoxycorticosterone acetate of constant surface area and hardness has been determined in 15 dogs and in 12 human beings. Similar studies have been made with 75 mg. pellets of testosterone and with 15 mg. pellets of estradiol benzoate in human beings. Experiences with pellets of testosterone implanted within the testicle of 2 human beings will also be detailed.

The over-all time for the absorption of the pellets of desoxycorticosterone acetate was between 10 and 12 months with an average daily absorption per pellet of 0.24 mg. The average period over which patients experienced symptoms was approximately 9 months.

Pellets of testosterone propionate were absorbed at the rate of approximately 0.3 mg. per pellet per day in both the dog and the human being, with an over-all absorption time of 8 to 9 months. Periods of symptomatic relief varied from 2 to 8 months.

Pellets of estradiol benzoate were absorbed at an average rate of about 0.05 mg. per pellet per day with a calculated over-all absorption time of approximately one year. Periods of subjective relief varied from 3 to 9 months.

About the area of testicular implant in one human being there was an active regeneration of testicular tissue. In the other no trace of seminiferous tubules could be found at autopsy some 3 months after a third implantation of 225 mg. of testosterone propionate.

It has been shown that 1.0 mg. desoxycorticosterone acetate absorbed daily from an implanted pellet is the equivalent in activity of approximately 5 mg of the material in a sesame oil medium administered daily by subcutaneous injection. Approximately the same ratio holds for the implantations of testosterone propionate. Sufficient data have not been accumulated to determine the conversion equivalents of implanted pellets of estradiol benzoate in terms of periodic injections in an oil medium, but it has been possible to produce full estrogenic responses in the vaginal smear from a single 15 mg. pellet.

The number of pellets implanted has no relation to the rate of absorption of the individual pellet. Towards the end of the absorption period there is a decrease in the rate of assimilation, but this is not appreciable for the first five months after implantation. However, it seems unlikely that the decreased absorption is the only factor involved in the return of symptoms and signs of hormonal insufficiency prior to the end of the absorption period.

49. Absence of Renotropic Action of Pure Adrenocorticotropic Hormone (ACTH).

Miriam E. Simpson, Choh Hao Li, and Herbert M. Evans. Institute of Experimental Biology, University of California.

Reiss has recently reported (Reiss, M.: *Nature (London) 154:* 737, 1944) in-

creased kidney weights in young rats acutely treated with a purified pituitary adrenocorticotropic preparation. The conditions of his experiment have been duplicated as closely as possible in an effort to test whether electrophoretically homogeneous ACTH would have the same effect. It was not possible to show changes in renal histology or significant increases in the kidney weights.

50. The Rate of Metabolism of Steroid Hormones by the Livers of Different Species.

L. T. Samuels and C. J. McCauley. Department of Biological Chemistry, University of Utah, Salt Lake City.

The rate of destruction of testosterone and esterone and estrogens has been studied after incubation with liver mince, using chemical methods of estimation. Liver tissue of the human, rat, mouse, rabbit and dog have been used. The rate of destruction is lowest in the human liver and the most rapid with rat and mouse livers. There appears to be no correlation between the rates of destruction of estrone and of testosterone. The bearing of these results on the reactions in different species will be discussed.

51. The Comparative Effect of Various Goitrogenic Agents on the Collection of Radioactive Iodine by the Thyroid in Rats and Chicks.

Rulon W. Rawson, D. A. McGinty and Wendell Peacock. From the Thyroid Clinic of the Massachusetts General Hospital, Boston; the Research Laboratories of Parke Davis & Company, Detroit; and the Nuclear Physics Laboratories, Massachusetts Institute of Technology, Cambridge.

The collection of radioactive iodine by the Thyroids of chicks and rats treated acutely and chronically with various goitrogenic compounds has been compared.

All of the agents studied were alike in preventing the collection of radioactive iodine administered one to six hours after a single injection of the various drugs. However, when administered chronically these agents differed radically in their effects. Thiouracil and related compounds blocked the collection of iodine in both rats and chicks. Amino mercaptothiadiazole and phenylaminomethyl mercaptothiazoline blocked the collection of iodine in rats, but caused an increase in the collection of iodine in chicks. Potassium thiocyanate increased the collection of iodine in rats.

It is concluded that various goitrogenic agents produce their effects on the thyroid through different mechanisms and that the effects produced with such agents vary with the species.

52. Turner's Syndrome: A Case Report.

William M. Moffat. Santa Barbara.

Since the syndrome of infantilism, congenital webbed neck and cubitus valgus in females was first described by Henry H. Turner in 1938 based upon a collection of 10 cases, only 6 cases presenting the entire triad have been published.

This report describes the case of a 21 year old girl of above average intelligence. She is 62¾ inches in height. She has a web of skin extending from behind each ear to the shoulder. The posterior surfaces of these webs are covered with thick hair. She has cubitus valgus. The external genitalia are undeveloped; no uterus is palpable and the cervix is about 5 mm. in diameter. No glandular tissue can be felt in her breasts which are rudimentary with small areolae and no nipples. Her hips are flat like a boy's. Her skin displays many pigmented moles. Vaginal smears show that the mucosal cells are completely lacking in glycogen. X-ray studies show an epiphyseal development of 16 years of age. The relationship of Turner's Syndrome to other reported syndromes presenting some of the same features is discussed.

53. Influence of Metabolism on Enuresis.

Robert M. Oslund. Ross-Loos Medical Group, Los Angeles.

Nocturnal enuresis appears to be a functional disturbance resulting from or accompanying low metabolism.

Patients ranging in age from 3½ to 19 years, studied for abnormal physiological bone age, were not indicative. Basal metabolic readings were usually only slightly

below normal; however, thyroid given to these patients produced cessation of nocturnal enuresis within two to three weeks; similar results although not as rapid, may be obtained from pituitary material.

As a great many hypothyroid patients do not experience nocturnal enuresis, the results are therefore interpreted as purely metabolic and not a thyroid deficiency.

54. Quantitative Inhibition of Oestrogen Effect on Chick Oviduct by Progesterone.

Roy Hertz. National Institute of Health, Bethesda, Md.

Inhibition of estrogen-induced weight increase in the chick oviduct by simultaneously administered progesterone is proportional to the progesterone dosage up to a maximum, beyond which even a six-fold increment in progesterone level effects no further inhibition. In the presence of a maximally effective progesterone dosage a sixteen-fold increase in estrogen dosage does not overcome the progesterone inhibition. Preliminary administration of maximally effective doses of progesterone for two days prior to the initiation of estrogen treatment does not enhance the degree of inhibition obtained.

Homogenates of the oviduct from chicks treated with an inhibitory combination of estrogen and progesterone are without effect upon the estrogen response in the chick. Additional studies on the mechanism of the estrogen-progesterone antagonism will be reported.

55. The Effect of Subcutaneous Administration and Topical Application of Steroid Preparations to the Pigmentation Area of the Hamster.

Herbert S. Kupperman. Department of Endocrinology, University of Georgia School of Medicine, Augusta.

In the costo-vertebral area of the golden hamster an area of excessive melanin deposition has been observed in the adult male hamster. This area is about 0.5 cm. in diameter, also associated with an increased amount of coarseness of the pellage. Pigmentation is absent or diminished in immature and adult females, immature and castrated males, and is of decreased intensity in senile males. Pigmentation and coarseness of the tuft of hair may be induced by topical application or subcutaneous administration of androgenic preparations. Estrogen, progesterone and desoxycorticosterone have a suppressing effect on the pigmented area. Simultaneous administration of androgen and estrogen to castrated males produces essentially the same effect as androgens alone, thus failing to demonstrate antagonism between folliculoid and android hormones. The relative effectiveness of the steroid preparation in producing pigmentation in the castrated male or female is closely correlated with the android activity of the preparation. The topical application of alcoholic solution of male hormone as a means of assay for android activity is discussed.

56. The Influence of the Adrenal Cortex on the Metabolism of the Eviscerated Rat.

Sidney Roberts. From the Worcester Foundation for Experimental Biology, Shrewsbury.

Adrenalectomy following evisceration in the fasted rat produced a 50 percent reduction in survival time and an increased rate of blood sugar disappearance. Upjohn cortical extract in oil had a small moderating effect. Other extracts tested were still less active. Since estrogens have been found to be inactive under similar circumstances (Szego & Roberts, Endocrinology *36:* 104, 1945), the viscera may be essential for the complete activity of steroid hormones in general.

Adrenalectomy in the eviscerated rat did not influence:

(1) rate of rise of blood amino acids,

(2) rate of fall of blood volume,

(3) simultaneous renal arterio-venous (A-V) differences for sugar, amino acids, and hemoglobin.

Simultaneous analyses of tail and aortal blood samples for sugar revealed that

adrenalectomy uniformly produced an increased peripheral A-V difference. This might be due to more rapid sugar utilization. Other considerations, however, indicate that the primary effect of adrenalectomy in the eviscerated rat is hemodynamic, and that the increased peripheral A-V difference reflects an increased circulation time. The circulatory changes include a reduction in renal blood flow, which suggests that the actual rate of gluconeogenesis in the kidney is reduced by adrenalectomy even though renal A-V differences for sugar are unchanged.

57. The Nature of Benadryl Activity: Glucose Tolerance Curves.

Herman Reinstein and T. H. McGavack.
N. Y. Medical College, Metropolitan Hospital Research Unit.

Intravenous glucose tolerance curves have been performed by standard techniques on 17 subjects ranging in age from 21–71 years. Each patient was maintained on a diet of 2300 calories, containing 200 gm. of carbohydrate, 95 gm. of protein, and 125 gm. of fat, for 3 days before the performance of the first glucose tolerance test and throughout the entire period of study except on the days during which tests were taken. Three tests were done on each subject: one without Benadryl (Curve I), one beginning one-half hour following the ingestion of 400 mgm. of Benadryl orally (Curve II), and the third, one-half hour following the administration of 30 mgm. of Benadryl intravenously (Curve III). The results of each of the three tests have been averaged for the 14 patients. In each instant a composite curve was drawn; the first and second of these composite curves closely approximate each other. However, it was noted that in younger individuals the area of the curve obtained following Benadryl orally was significantly larger than that of the control, whereas in older individuals, above 50, the reverse was true. Following the use of Benadryl intravenously (Curve III) there was a significant increase in sugar tolerance in all subjects irrespective of age, as shown by a decrease in the areas of the individual and composite curves respectively. In order to rule out any normal variation in glucose tolerance when determined at three day intervals, three subjects were given the same regime as the 14 test subjects mentioned above except that no medication was used in conjunction with any of the three tests obtained per subject. It is significant that in each of these three subjects curves of smallest area were obtained in the first test with a moderate but sigfinicant increase in the area with each of the two succeeding examinations.

These findings will be discussed in relation to the nature of the action of Benadryl and its antihistamine effects.

58. Nature and Distribution of the Skeletal Abnormalities in Cushing's Syndrome.

Fuller Albright, Anne P. Forbes, and Edward C. Reifenstein, Jr. Dept. of Medicine, Harvard Medical School and Massachusetts General Hospital, Boston.

It is pointed out that the demineralization of the bone in Cushing's Syndrome is the result of osteoporosis. By "osteoporosis" is meant that bone condition where the primary abnormality is a failure of the osteoblasts to lay down matrix.

The osteoporosis in Cushing's Syndrome has a marked predilection for the spine and pelvis. A case of Cushing's Syndrome in a girl of thirteen is presented. The x-rays of the bone before and after the condition was alleviated are most instructive.

The effect of potassium on the calcium balance of two cases of Cushing's Syndrome are presented.

59. Management of Threatened and Habitual Abortion by Large Doses of Oral Estrogen.

A. R. Abarbanel. Department of Obstetrics and Gynecology College of Medical Evangelists, Los Angeles.

Fifty cases of threatened and habitual abortion were treated by means of oral estrogen (diethylstilbestrol) in doses ranging from 15 to 500 mg. daily. The homostatic effect was evident in 4 to 24 hours.

A large percentage of fetuses were salvaged. It is felt that the effect of estrogen

upon the endometrial vascular bed, particularly at the site of placentation, is responsible for the favorable clinical results.

60. Clinical Syndromes of Aberrations in Corpus Luteum Function.

Virgil O. Parret and A. R. Abarbanel. From Department of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles.

The following syndromes which are felt to stem from aberrations of corpus luteum function are briefly presented and correlated with the pathological findings:

Hemorrhage into corpus luteum (simulating an acute surgical abdomen).
Persistent corpus luteum simulating ectopic pregnancy.
Lutein cysts resembling chocolate cysts of endometriosis.
Persistent corpus luteum causing prolonged amenorrhea of several years.
Luteinized thecoma and also luteoma causing masculinization syndrome.

61. Problem of "Closed Fallopian Tubes" Hormonal Differentiation of Tubes Closed by Spasm from Those Closed by Organic Pathology by Means of Methyl Testosterone.

A. R. Abarbanel. Department of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles.

Twelve patients, who were diagnosed as having "closed tubes" and advised that they were now sterile, were given oral methyl testosterone, 5 mg. sublingually per day for one to three months. In each case the tubes were then found to be patent. In four cases pregnancy ensued during therapy.

The modus operandi is discussed.

62. The Use of Sodium Para-Aminobenzoate Parenterally in the Treatment of Hyperthyroidism.

Louis Berman, N. Y. City.

In a preliminary communication to the Sodiety for Experimental Biology and Medicine in May, 1945, a report was presented of beneficial therapeutic effects obtained in six ambulatory cases of hyperthyroidism by the parenteral administration of one gram or larger doses of the sodium salt of para-aminobenzoic acid six times weekly over a period of months with no unfavorable by-effects such as have been reported by clinicians employing thiourea and thiouracil. Eight more cases of hyperthyroidism so treated will be reported.

The treatment of the first case was begun in 1943, a patient with hyperthyroidism complicated with vitiligo to whom the sodium salt was administered as an attempt to influence the skin pigmentation disturbance. The oral use of para-aminobenzoic acid by itself and as a supplement to the parenteral administration of its sodium salt will also be discussed. Observations of the effects on pulse, blood pressure, weight, basal metabolism, blood cholesterol and the clinical symptoms and course of the disease will be presented. The details of the eight other cases will be given in addition to further observations on the six originally treated and followed up.

63. Hypogonadotrophic Enuchoidism—Its Clinical and Laboratory Delineation from Other Forms of Hypogonadism with a Discourse on Treatment.

Carl G. Heller and Warren O. Nelson. Departments of Physiology and Medicine, University of Oregon Medical School, Portland, and Department of Anatomy, University of Iowa, Iowa City.

Gonadotrophic hormone assays and testicular biopsies were found to be the most reliable laboratory criteria for establishing the diagnosis of hypogonadotrophic eunuchoidism. After laboratory classification it was possible to delineate this group from other forms of eunuchoidism by clinical means and by use of a therapeutic test.

Successful correction occurred following administration of chorionic gonadotrophin and a purified follicle stimulating hormone (prepared by McShan). Response was judged by clinical improvement and laboratory and serial biopsy changes.

64. Determination of Corticosteroids in Urine.

B. E. Lowenstein, A. C. Corcoran, and Irvine H. Page. From the Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio.

The present method is based on periodate oxidation (Fieser, Fields and Lieberman) of the primary alcohol group at C_{21} which yields one mol of formaldehyde per mol of corticosteroid oxidized. Formaldehyde is then determined by the method of MacFadyan.

Procedure: To a 3 cc. aqueous aliquot of a urinary extract (Venning, Hoffman and Browne) is added 0.1 cc. of 0.05 M HIO_4 in 0.3 N H_2SO_4. Oxidation proceeds at about 25°C for 20 minutes when it is arrested by addition of 0.1 cc. of 6 per cent $SnCl_2$. Five cc. of 0.2 per cent chromotropic acid (Eastman) in 15 M H_2SO_4 are added and the mixture heated for 30 minutes at 100°C. The cooled solution is made up to 12.5 cc. by addition of 9 M H_2SO_4 and color density read in the Coleman Model 6 spectrophotometer.

The method gives good recoveries from urine samples containing added cortical extract. The average excretion of corticosteroids in normal males is .5–.8 mg. per 24 hours, expressed as dehydrocorticosterone. In a case of Addison's disease, the value was 0.15 mg. and in one of Cushing's syndrome, 21 mg. per 24 hours.

The advantages of the method lie in simplicity, lack of urinary "blank" and in that the estimates include both active and partially reduced corticosteroids.

65. The Effect of Hypophysectomy on the Time of Lay of the Hen's Egg.

Irving Rothchild (Introduced by Richard M. Fraps). U. S. Department of Agriculture, Agricultural Research Center, Beltsville, Maryland.

Delays in lay occurred in Rhode Island Reds and White Leghorns, after either complete or partial hypophysectomy performed either on the day of ovulation or on the day of expected lay; no delays however, occurred after sham hypophysectomy. The distribution of results according to breed, completeness of operation, and time of operation was as follows:

	Rhode Island Reds	White Leghorns
Complete hypophysectomy on day of ovulation	delays in 12 out of 25 birds	delays in 9 out of 27 birds
Complete hypophysectomy on day of expected lay	delays in 4 out of 9 birds	delays in 1 out of 10 birds
Partial hypophysectomy on day of ovulation	delays in 8 out of 20 birds	delays in 1 out of 7 birds
Partial hypophysectomy on day of expected lay	delays in 2 out of 5 birds	delays in 2 out of 3 birds
Sham hypophysectomy on day of ovulation	no delays in 16 birds	no delays in 15 birds
Sham hypophysectomy on day of expected lay	no delays in 4 birds	

These data indicate that removal of or injury to the AP results in partial interference with the determination of the time of normal lay. The nature of AP participation in the process of lay is under further investigation.

66. Parathyropituitary Syndrome in Pituitary Basophilism.

Robert M. Perlman. San Francisco.

Pathologic bone changes are an almost invariable accompaniment of pituitary basophilism. In earlier papers discussion centered around the probability that such changes are the result of a "primary" pituitary malady which secondarily affects the parathyroid glands, upsetting the calcium metabolism, and thereby leading to disturbances in bone structure. It was shown that an intricate parathyropituitary relationship also occurred in pituitary eosinophilism, resulting in a definite symptom-complex which was later described as the "Parathyropituitary Syndrome in Pituitary Eosinophilism." Altogether special mechanisms must enter into play when basophilic hyperpituitarism occurs simultaneously with hyperparathyroidism. Such mechanisms must be investigated separately and interpreted clearly; hence, *raison d'être* for this present paper.

Substantial evidence is presented in the body of this paper to indicate that the basophilic version of the parathyropituitary syndrome may find expression in either of two extreme or a multitude of intermediate forms: 1) Cushing's syndrome in its banal form, with relatively mild skeletal destruction ("osteoporosis and osteomalacia" leading to scoliosis, kyphoscoliosis, lordosis, etc.). 2) Cushing's syndrome complicated by an accentuated osteoclastic skeletal resorption and fibrous neoformation of osseous tissues. These processes can become intense enough to render the full-fleged, typical, clinical and anatomical picture of von Recklinghausen's bone disease complete with spontaneous fractures and adenomatous parathyroid hyperplasis. The Syndrome may express itself in varying degrees, and may be complicated further by the intervention of renal pathology.

67. Diurnal Variations in the Levels of Blood Glucose of Normal Human Beings Subjected to Various Types of Caloric Restriction.

David Schwimmer and Thomas H. McGavack. N. Y. Medical College, Metropolitan Hospital Research Unit.

Fifty-seven subjects have been divided into groups and given varying amounts of carbohydrate, protein, and fat with total caloric equivalents ranging from 900–1800 calories. The protein of the diet varied from 0–10% by weight. The subjects were fed at 9 A.M., 1 P.M., 5 P.M., and 9 P.M., with divisions of ⅛, ⅜, ⅜ and ⅛, respectively. The widest fluctuations in blood glucose were observed in subjects who received diets containing only carbohydrate and fat. This was true irrespective of what caloric equivalent was used. Many of the subjects on these diets showed hypoglycemic symptoms and the signs came on as a rule between one-half and two hours after the 1 P.M. feeding. Simultaneously, levels for blood sugar dropped to levels as low as 50 mgm. per 100 cc. Sources of protein supplements were malted milk, lactalbumin, and dried egg white. The amino-acid methionine was similarly tried in lieu of and with protein. Methionine alone had no significant influence on the blood sugar trend. All forms of protein decreased the range of variation in the levels for the glucose of the blood.

When the above findings were brought into relation with data simultaneously procured regarding urinary volume, solutes, nitrogen balance, electrolyte balance and so forth, it was concluded that protein may serve a very useful purpose as a part of restricted rations.

68. The Role of Sex Hormones in the Origin and Development of Endometrial Glands in the Opossum.

Carl R. Moore and Elizabeth A. Failor. Hull Zoological Laboratory, The University of Chicago.

In the young opossum uterine development is slow hence is excellent for the determination of sex hormonal influences. Muellerian ducts are formed between postnatal days 3 and 10; oviducts, uterus and lateral vaginal canals are distinguishable by day 30. Uterine growth and differentiation continue progressively and by day 80 the smooth epithelial lining changes to low villi and shallow crypts. Endometrial glands arise as balls of cells from base of crypts about days 85–95 and hollow out into small flask-shaped glands by day 100. Rapid gland formation and elongation characterize postnatal days 100–140.

Bilateral ovariectomy on day 20 fails to delay uterine differentiation up to the time of usual gland formation (days 85–95) but it does prevent gland formation. Ovariectomy from days 80 to 95 causes a cessation of gland development even when glands are in process of development at operation.

Androgens as well as estrogens stimulate endometrial gland formation precociously as early as day 40 but sensitivity of the uterus to respond increases as the time of gland formation is approached.

It becomes clear that 1) endometrial gland formation and development is a function of estrogenic hormones from the ovary; 2) this is not an estrogen specific response but occurs with androgens; 3) the earliest detectable ovarion secretion occurs around days 85–95; 4) early uterine differentiation does not depend upon secretions from the developing ovary.